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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

AMGEN INC., Plaintiff, v. SANDOZ INC., et al., Defendants.	Civil Action No. 18-11026 (MAS)(DEA) (consolidated) Hon. Michael A. Shipp, U.S.D.J. Hon. Douglas E. Arpert, U.S.M.J.

PLAINTIFF AMGEN'S POST-TRIAL BRIEF

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TABLE OF ABBREVIATIONS

'101 Patent	U.S. Patent No. 7,893,101 (JTX-0005), an asserted patent which is directed to crystalline Form B of apremilast.
'283 Patent	U.S. Patent No. 8,093,283 (JTX-0006), an asserted patent which is directed to crystalline Form A of apremilast.
'536 Patent	U.S. Patent No. 8,455,536 (JTX-0007), an asserted patent which is directed to a method of using stereomerically pure apremilast to treat psoriasis.
'541 Patent	U.S. Patent No. 10,092,541 (JTX-0013), an asserted patent which claims methods of treating a patient suffering from psoriasis with apremilast according to a specific schedule that involves dose titration.
'638 Patent	U.S. Patent No. 7,427,638 (JTX-0003), an asserted patent which is directed to pharmaceutical compositions comprising stereomerically pure apremilast.
'940 Patent	U.S. Patent No. 6,962,940 (JTX-0001)
'358 Patent	U.S. Patent No. 6,020,358 (DTX-174)
'049 Publication	International Patent Application Publication WO 2003/080049 (DTX-189)
'052 Publication	U.S. Patent Application Publication 2003/0187052 A1 (DTX-179)
'515 Provisional	U.S. Provisional Application No. 60/366,515 (JTX-0043)
Amgen	Amgen Inc., the Plaintiff in this litigation.
ANDA	Abbreviated New Drug Application
API	active pharmaceutical ingredient
Asserted claims of the '638 Patent	Claims 3 and 6 of the '638 Patent
Asserted claims of the '536 Patent	Claim 6 of the '536 Patent

Asserted claims of the '101 Patent	Claims 1 and 15 of the '101 Patent
Asserted claims of the '283 Patent	Claims 2 and 27 of the '283 Patent
Asserted claims of the '541 Patent	Claims 2, 19, and 21 of the '541 Patent
Brittain 1997	Brittain, H.G., *Spectral Methods for the Characterization of Polymorphs and Solvates*, 86(4) J. Pharm. Sci. 405–12 (1997) (DTX-98)
Brittain 1999	Brittain, H.G., Methods for the Characterization of Polymorphs and Solvates, in Polymorphism in Pharmaceutical Solids (H. Brittain ed., Vol. 95 1999) (DTX-99)
Byrn 1994	Byrn, S.R. et al., *Solid-State Pharmaceutical Chemistry*, 6 J. Chem. Materials 1148–58 (1994) (DTX-101)
CC-7085	The internal designation of a racemate compound prepared by Celgene. The external designation for CC-7085 was CDC-998; but the connection among CDC-998, CC-7085 and its structure was not publicly known as of the priority date of the '638 Patent.
CDC-801	Celgene Developed Compound No. 801, also known as CC-1088
Celgene	Celgene Corporation, the former plaintiff in this litigation.
COPD	chronic obstructive pulmonary disease
Defendants	Collectively, Sandoz Inc., and Zydus Pharmaceuticals (USA) Inc.
Dyke 1999	Dyke, A. et al., *The therapeutic potential of PDE4 inhibitors*, 8(9) Exp. Opin. Invest. Drugs 1301–25 (1999) (JTX-0067)
EPO	European Patent Office
FDA	United States Food and Drug Administration
Fieser	"Crystallization," Organic Experiments (Fieser, L. & Williamson, K. eds., 3d ed. 1975) (JTX-0178)

Guillory	Guillory, J.K., *Generation of Polymorphs, Hydrates, Solvates and Amorphous Solids*, 95 Polymorphism in Pharmaceutical Solids 183–226 (Brittain ed., 1999) (DTX-125)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH Guidelines	ICH Harmonised Tripartite Guideline, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (1999) (DTX-128)
IND	Investigational New Drug
JSF	Citation to Joint Stipulated Facts in Section III of the Pre-trial Order (ECF No. 422)
Marriott 2001	Marriott, J. et al., *Immunotherapeutic and antitumor potential of thalidomide analogues*, 1(4) Expert Opin. Bio. Ther. 675–82 (2001) (DTX-129)
Muller 1998	Muller, G. et al., *Thalidomide Analogs and PDE4 Inhibition*, 8 Biorg. Med. Chem. Lett. 2669–74 (1998) (JTX-0069)
NDA	New Drug Application
ODP	Obviousness-type Double Patenting
Papp 2012	Papp, K. et al., *Efficacy of Apremilast in the Treatment of Moderate to Severe Psoriasis: A Randomised Controlled Trial*, 380 The Lancet 738–46 (2012) (DTX-153)
Patent Office	United States Patent and Trademark Office
Pathan	Pathan, E., et al., *Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis*, Annals of the Rheumatic Diseases, 0:1-6 (2012) (DTX-157)
PDE4	Phosphodiesterase IV
PDE4A4	Isoform of PDE4, affinity for which used to

	calculate a ratio for PDE4 inhibitors
PF	Citation to Plaintiff's Findings of Fact, submitted concurrently with this brief
Plaintiff	Amgen Inc.
POSA	Person of Ordinary Skill in the Art.
PTA	Patent Term Adjustment
PTE	Patent Term Extension
Sandoz	Sandoz Inc., a Defendant in this litigation.
Schett 2012	Schett, G. et al., *Oral apremilast in the Treatment of Active Psoriatic Arthritis*, 64(10) Arthritis & Rheumatism 3156–67 (Oct. 2012) (DTX-162)
SelCID	Selective Cytokine Inhibitory Drug, a thalidomide analog class developed by Celgene
SSF (A3)	Citation to Sandoz's Stipulated Facts in Exhibit A3 to the Pre-trial Order (ECF No. 422)
Takeuchi	Takeuchi, Y., et al., *(R)- and (S)-3-Fluorothalidomides: Isosteric Analogues of Thalidomide*, 1(10) Organic Letters 1573 (1999) (DTX-168)
TNF	Tumor Necrosis Factor
WO '102	International Patent Application Publication WO 2011/063102 (DTX-194)
WO '606	International Patent Application Publication WO 01/34606 (DTX-159)
WO '777	International Patent Application Publication WO 2000/25777 (JTX-0264)
XRPD	X-ray Powder Diffraction
ZSF (A2)	Citation to Zydus's Stipulated Facts in Exhibit A2 to the Pre-trial Order (ECF No. 422)
Zydus	Zydus Pharmaceuticals (USA) Inc., a Defendant in this litigation.

INTRODUCTION

Celgene scientists made a number of breakthrough inventions in bringing a new medicine, Otezla®, to patients with psoriasis. These inventions are set forth in the claims of the patents-in-suit: a pharmaceutical composition of stereomerically pure apremilast for oral administration (the '638 Composition Patent), methods for treating psoriasis patients with apremilast (the '536 Psoriasis Patent), crystalline forms of apremilast (the '101 Form B Patent and '283 Form A Patent), and a universal dose titration schedule for patients new to apremilast treatment (the '541 Titration Patent). The evidence showed that each of these inventions was novel and not obvious, and that Defendants failed to meet their heavy burden to prove otherwise.

In a crowded field of researchers, including many larger competitors, all seeking to find a therapeutic that would inhibit PDE4, only one company succeeded in creating a new oral medicine to treat psoriasis—Celgene, a small company from New Jersey. Celgene took the unusual and risky path of attempting to develop medicines from analogs of the notorious compound thalidomide—even though nobody understood at the time ***why*** thalidomide was so toxic. After years of effort, Celgene created apremilast, a selective PDE4 inhibitor and thalidomide analog that surprisingly overcame thalidomide's toxicity and also avoided the dose-limiting side effects that had plagued the entire class of PDE4 inhibitors. Apremilast proved to be unexpectedly more potent, with a higher therapeutic index than the leading PDE4 inhibitor in development at the time. Celgene's inventions resulted in the medicine Otezla, which met the need for a safer, effective treatment for the most common form of psoriasis, plaque psoriasis.

Even after these inventions, there remained a desire to further mitigate the side effects some psoriasis patients encounter when they are new to taking apremilast. Eschewing the conventional approach of individualized, feedback-driven dose titration, one Celgene scientist invented a

universal dose-titration schedule for apremilast that has since been approved by FDA and is reflected in the asserted claims of the `541 Titration Patent.

Attracted by the commercial success of Otezla, nineteen generic companies sought to enter the market with generic copies of Otezla. Seventeen of those companies have now settled and acknowledged the validity of Amgen's patents. Two defendants, Sandoz and Zydus, remain in the case. With one exception,[1] Sandoz and Zydus have admitted infringement of each asserted claim.

Defendants instead challenge the validity of the asserted claims. But patent claims are presumed valid, 35 U.S.C. § 282, and thus Defendants bear the burden of proving the asserted claims invalid by clear and convincing evidence.[2] *Microsoft Corp v. i4i Ltd. P'ship*, 564 U.S. 91, 95–97 (2011). In trying to meet this burden, Defendants relied almost entirely on prior art already considered by the Patent Office when it granted the asserted claims. For example, the Patent Office already considered the '358 Patent during the examination of the applications leading to the '638 Composition and '536 Psoriasis Patents, and yet it is the centerpiece of Defendants' anticipation and obviousness challenges. Before granting the '541 Titration Patent, the Patent Office considered the same obviousness combination of Papp 2012, Schett 2012, and the '536 Patent Defendants advance here. "[A] party challenging validity shoulders an enhanced burden if the invalidity argument relies on the same prior art considered during examination by the U.S. Patent and Trademark Office[.]" *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011). The evidence at trial showed that Defendants failed to meet their burden.

[1] Zydus disputes infringement of Claims 1 and 15 of the '101 Patent. *See infra* Section II.A.1.

[2] Defendants have been quick to cast aspersions in this trial, accusing Amgen of "blocking" them from entering the market through the purported assertion of a "thicket" of invalid patents that "extend" a patent monopoly for "over a decade." It bears noting that Defendants' rhetoric is untethered to any counterclaim or defense of misconduct, and appears designed to distract from the substantive weakness of Defendants' case.

In arguing anticipation of the ’638 Composition and ’536 Psoriasis Patents, Defendants rely on the prior art ’358 Patent, which discloses only racemic mixtures of stereochemical compounds. Ignoring the law and the facts here, Defendants and their witnesses wrongly assume that the disclosure of the racemate provides the stereomerically pure enantiomer and therefore anticipates the claimed inventions, which it does not. The Federal Circuit has made clear that the disclosure of a racemate does not anticipate later claims to a pure enantiomer, *see Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1084 (Fed. Cir. 2008), and applies the legal test of whether the individual enantiomer has been “separated, identified and characterized” in the prior reference. Defendants’ evidence does not come close to satisfying this test. Defendants’ witnesses provided no evidence of how the claimed stereomerically pure apremilast could be obtained from the disclosure of the ’358 Patent, let alone show that it was inherent in the ’358 Patent’s disclosure.

On obviousness, Defendants’ evidence fell far short of their clear and convincing burden. Defendants’ witnesses continually engaged in improper use of hindsight. Defendants’ counsel provided select references for their experts to opine on. Those experts then gave conclusory opinions based on a limited set of facts and assumptions. For example, in arguing obviousness of the ’638 Composition and ’536 Psoriasis Patents, Defendants worked backwards, looking for a structurally similar compound to apremilast in the prior art and finding the racemate of Example 12 of the ’358 Patent even though the POSA would have had no reason to be interested in that compound. There was no biological data for Example 12 or any of the compounds in the ’358 Patent, as opposed to the many other prior art compounds for which robust biological data was available. To guard against such impermissible hindsight, the case law provides the “lead compound analysis” which starts with the selection of the compound that a chemist would have considered the “most promising” for further development. The selection of the “lead compound”

is guided by the properties of the compound, such as potency or toxicity, and is not based on structural similarity. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–92 (Fed. Cir. 2012). But Defendants did not even attempt to apply or meet that test. Similarly, with respect to the '541 Titration Patent, Defendants argued that the POSA would have modified the Papp 2012 schedule by one day to arrive at the asserted claims, ***not*** because that particular modification would have made any sense in light of the prior art, but because the '541 Titration Patent claims a six-day titration schedule.

In contrast to the conclusory opinions of Defendants' experts, Amgen's experts provided the proper perspective for how the POSA would view the prior art as a whole and what would be possible or not. For example, Amgen's experts explained why the POSA would have been hesitant to develop a thalidomide analog for the treatment of patients, specifically psoriasis patients, given thalidomide's tragic history and the reality that the POSA did not know why thalidomide was teratogenic. Defendants attempted to counter this perspective largely by observing that the 1960s were a long time ago and that thalidomide was subsequently approved for limited use to treat ENL, a form of leprosy with no other treatment options. But such arguments provide no reasons why the POSA would have been motivated to take on additional risk of failure with analogs of a notoriously toxic compound—particularly when so many other PDE4 inhibitors, with robust safety and efficacy data, were being investigated and did not present such a risk.

Similarly, every significant aspect of the opinion of Defendants' expert for the `541 Titration Patent, Dr. Gilmore, was lacking in record support. For example, Dr. Gilmore opined that the POSA would have focused on the Papp 2012 five-day titration schedule, and used that as a starting point to design a titration schedule for use in treating psoriasis. But she never explained *why* the POSA would have favored a titration schedule constrained by the artificial circumstances

of a clinical trial over the prior art's consistent teaching that titration is done on an individualized, feedback-driven (and prolonged) basis. Indeed, Dr. Gilmore never addressed that art, even to explain why she thought it was inapplicable. Dr. Gilmore next opined that the POSA would have modified the Papp 2012 schedule to arrive at the asserted claims. But Papp 2012 itself reported that, in the opinion of the authors, apremilast was "well tolerated." Dr. Gilmore did not explain why the POSA would have extended the titration by only a single day—Papp 2012 states that tolerability issues persisted for multiple weeks and up to a month during the study. Finally, Dr. Gilmore opined that the POSA would have only considered titration schedules of one week or less based on an alleged need in the "clinical trial environment" to begin collecting data quickly. Dr. Gilmore was neither tendered nor accepted as an expert in clinical trial design, and Dr. Gilmore pointed to no documents referencing, much less supporting, this alleged urgent need for data collection as driving the POSA's decisionmaking. She also made no attempt to reconcile this opinion with the prior art which consistently taught the practice of *multi-week* titration. The reason Dr. Gilmore could not ground these opinions in the prior art is because the opinions reflect her hindsight bias. Conclusory expert opinions are simply insufficient to carry Defendants' burden.

Defendants' burden cannot be met by hindsight-driven analyses of the prior art, unsubstantiated expert opinions, conflicting evidence, or hyperbolic attorney argument. Amgen asks for judgment finding each asserted claim is infringed by each Defendant and not invalid.

ARGUMENT

I. The Asserted Claims of the '638 Composition and '536 Psoriasis Patents Are Infringed and Not Invalid.

The parties' disputes concerning the '638 and '536 Patents are limited to validity, as both Sandoz and Zydus have stipulated to infringement of the asserted claims of both patents. PF ¶¶ 265-269. For the reasons set forth below, Defendants have not met their burden to prove that

the asserted claims of the ’638 and ’536 Patents are invalid as anticipated or obvious.

A. Defendants Have Not Shown That the Asserted Claims of the ’638 Composition Patent and ’536 Psoriasis Patent Are Anticipated.

Stereomerically pure apremilast is a required element of each asserted claim of the ’638 and ’536 Patents. Because stereomerically pure apremilast is neither disclosed nor enabled by the ’358 Patent, Defendants have failed to show by clear and convincing evidence that the asserted claims are anticipated by the ’358 Patent. Indeed, that burden is particularly difficult to meet here, where the ’358 Patent was considered by the Examiner during prosecution of the application that led to the ’638 Patent, and found to not disclose apremilast. PF ¶¶ 306–307.

1. The Law of Anticipation.

To anticipate, a single prior art reference must disclose all elements of the asserted claims, arranged as in those claims. *SRI Int’l, Inc. v. Cisco Sys., Inc.*, 930 F.3d 1295, 1306 (Fed. Cir. 2019). In cases involving enantiomers, an enantiomer is not anticipated by the prior art disclosure of a racemate if that enantiomer has not been “separated, identified, and characterized” in a prior art reference. *Sanofi-Synthelabo v. Apotex,* 550 F.3d 1075, 1084 (Fed. Cir. 2008); *see also UCB Inc. v. Accord Healthcare Inc.*, 890 F.3d 1313, 1330 (Fed. Cir. 2018) (following *Sanofi*, holding that “[a]lthough [the prior art] discloses the chemical structure of the [racemate], it does not disclose its separation into individual enantiomers nor does it disclose any pharmaceutical data of the . . . enantiomer recited [in the asserted claim]”), *id.* at 1330 (“We have also stated that ‘the novelty of an optical isomer is not negated by the prior art disclosure of its racemate’”) (*quoting In re May*, 574 F.2d 1082, 1090 (C.C.P.A. 1978))). In addition, to anticipate a reference must be enabling. *Forest Labs v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268 (Fed. Cir. 2007).

2. The ’358 Patent Does Not Disclose Stereomerically Pure Apremilast Under Controlling Federal Circuit Law.

The parties’ chemistry experts agree that stereomerically pure apremilast, a required

element of each of the asserted claims, is not separated, identified, or characterized in the '358 Patent. PF ¶¶ 342–367. The '358 Patent discloses Example 12, a racemate, which is a different compound than stereomerically pure apremilast, an enantiomer. PF ¶¶ 335–339. The experts also agree that the '358 Patent does not disclose any enantiomers—only racemic compounds. PF ¶¶ 343–344. Neither enantiomer of Example 12 is identified in the '358 Patent, and there is no information in the '358 Patent that either enantiomer of Example 12 had been prepared in stereomerically pure form separate from the racemate. PF ¶¶ 345, 355. The '358 Patent does not provide any characterization or biological data for stereomerically pure apremilast. PF ¶¶ 357–361. The '358 Patent also does not disclose stereomerically pure apremilast (1) with optical purity of greater than about 97% by weight, (2) in a pharmaceutical composition suitable for oral use, or (3) in a dose range of 10 to 200 mg, as required by the asserted claims of the '638 and '536 Patents. PF ¶¶ 362-364, 368–371.

Defendants attempt to cobble together a "disclosure" of apremilast by pointing to Example 12 and a general statement in the '358 Patent that the "compounds of Formula I possess a center of chirality and can exist as optical isomers . . . [t]he racemates can be used as such or can be separated into their individual isomers . . . ." DTX-174 at 8:63–9:3. But this general statement teaches nothing that the POSA would not have already known about Example 12. The parties' chemistry experts agree that the POSA would have appreciated this statement as a matter of general chemistry knowledge applicable to all of the billions of compounds of Formula I, and, indeed, any compound with a center of chirality. PF ¶¶ 349–351. In fact, Defendants' expert, Dr. Gribble, stated that his opinions regarding the purported disclosure of apremilast in the '358 Patent would be the same even if the '358 Patent did not contain this general statement. PF ¶ 352.

Under Federal Circuit case law, this general statement that the compounds of the '358

Patent can exist as optical isomers is not enough for anticipation. Indeed, this general statement is the same as the disclosure in the prior art at issue in *Sanofi* and merely reflects the "knowledge that enantiomers may be separated," which *Sanofi* held "is not anticipation of a specific enantiomer that has not been separated, identified, and characterized." *Sanofi*, 550 F.3d at 1084. The Federal Circuit's explanation in *Sanofi* illustrates the similarities to the case here:

> The court heard expert witnesses for both sides, who agreed that persons of ordinary skill in this field would have known that compounds that contain an asymmetric carbon atom have enantiomers. The [prior art patent] specification states: "These compounds having an asymmetrical carbon may exist in the form of two enantiomers. The invention relates both to each enantiomer and their mixture." . . . . However, as the witnesses agreed, all of the compounds in the [prior art patent] are racemates, and neither the twenty-one specific examples nor any other part of the specification shows their separation into enantiomers.
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> ***
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> The counterpart Canadian [prior art patent] states that when the desired structure is obtained it "is isolated and, if desired, its enantiomers are separated and/or it is saltified by mineral or organic acid action."
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> ***
>
> The district court did not clearly err in finding that the statements in the [prior art patent] and its Canadian counterpart that the products therein consist of enantiomers are not a description of the specific dextrorotatory enantiomer clopidogrel or a suggestion of its unusual stereospecific properties. ***The knowledge that enantiomers may be separated is not "anticipation" of a specific enantiomer that has not been separated, identified, and characterized.***

Id. at 1083–84 (emphasis added). Similar facts exist here. PF ¶¶ 342–367. Therefore, Defendants' anticipation theory fails.

Aware that binding Federal Circuit precedent requires more for anticipation than is provided by the '358 Patent, Defendants posit two alternative theories: one based on "inherency" and the other based on a "genus." But the Federal Circuit has already rejected the arguments that Defendants advance here. *See Sanofi*, 550 F.3d at 1083–84; *UCB*, 890 F.3d at 1330.

a. The '358 Patent does not inherently disclose stereomerically pure apremilast.

First, Defendants argue that stereomerically pure apremilast is inherently disclosed by the Example 12 racemate. This argument presents a scientific impossibility. A racemate, which by definition is a compound that is a 50/50 mixture of two enantiomers, cannot simultaneously be a stereomerically pure enantiomer substantially free of its opposite enantiomer. PF ¶¶ 373–374. Example 12 and stereomerically pure apremilast are two different and distinct compounds. PF ¶¶ 338–341, 372. One does not "inherently" disclose the other. In essence, Defendants argue that claims to an enantiomer should always be anticipated when the prior art discloses the racemate because the racemate consists of enantiomers. But the Federal Circuit expressly rejected that theory in *Sanofi*. 550 F.3d at 1084 ("The district court did not clearly err in finding that the statements in the [prior art] that the [racemic] products therein consist of enantiomers are not a description of the specific [claimed enantiomer] or a suggestion of its unusual stereospecific properties.")

Second, Defendants argue that following Example 12 and the general routes for making enantiomers in the '358 Patent (DTX-174 at 8:63–9:12) would have inherently—i.e., necessarily—produced stereomerically pure apremilast. But the Federal Circuit has made it clear that inherent anticipation requires more than a disclosure that something *may* or *can* be made. *See Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc.*, 344 F.3d 1186, 1192 (Fed. Cir. 2003) ("A claim limitation is inherent in the prior art if it is necessarily present in the prior art, not merely probably or possibly present."); *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981) ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient [for inherency]."). Here, the '358 Patent states that the "racemates can be used as such," DTX-174 at 8:67–9:1, which means that the POSA will not necessarily have an enantiomer; the POSA could use Example 12.

In any case, the POSA following the general routes for making enantiomers in the '358 Patent would not have necessarily obtained stereomerically pure apremilast. One of the general routes, chiral acid salt separation, cannot be applied to Example 12 and would ***never*** have produced stereomerically pure apremilast. PF ¶¶ 376, 386. Given the numerous decisions about which conditions to use for the other two general routes, chiral chromatography and asymmetric synthesis, those routes would not have necessarily produced stereomerically pure apremilast either. PF ¶¶ 388–391, 405–431.

b. The '358 Patent does not provide an anticipatory disclosure of stereomerically pure apremilast as a member of a "genus."

Defendants' final argument is that the racemate disclosed in Example 12 is actually a "genus" of three compounds—two enantiomers and a racemate—and the POSA would have "at once envisaged" stereomerically pure apremilast in that genus. But Defendants' characterization of the Example 12 racemate as a "genus" is incorrect as a scientific matter; a racemate is not a genus of enantiomer "species"; it is a different compound than its individual enantiomers. PF ¶¶ 338–341. Defendants' characterization of a racemate as a "genus" is also wrong as a matter of law. *See UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp. 3d 491, 544 (D. Del. 2016), *aff'd*, 890 F.3d 1313 (Fed. Cir. 2018) (rejecting Defendants' anticipation arguments in reference to "a line of cases holding that a prior art disclosure of a small genus anticipates each member of that genus" because "[the prior art racemate] is not a genus" and "[the claimed enantiomer] is not a 'species' or instance of [the prior art racemate]"). And even if Example 12 and its enantiomers are considered a genus, to prove anticipation under the "at once envisage" standard, Defendants would need to show "specific preferences" in the '358 Patent that would have directed the POSA to Example 12. *See Sanofi-Synthelabo v. Apotex Inc.*, 492 F. Supp. 2d 353, 385–86 (S.D.N.Y. 2007), *aff'd*, 550 F.3d 1075 (Fed. Cir. 2008) (finding no anticipation of a claimed enantiomer because the

prior art reference did not identify a specific preference that would guide the POSA to the relevant racemic compound and its enantiomers). However, there is no data in the '358 Patent and nothing that would have singled out Example 12 and its enantiomers. PF ¶¶ 315–333. Moreover, if either of Defendants' legal theories for anticipation were correct, an enantiomer would never be novel over the prior art disclosure of the racemate. Once again, that is not the law. *See, e.g.*, *Sanofi*, 550 F.3d at 1084 (holding that a prior art disclosure of a racemate did not anticipate claims to a specific enantiomer); *UCB*, 890 F.3d at 1330 (same); *In re May*, 574 F.2d at 1090 (same); *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 438 F. Supp. 2d 479, 486 (D. Del. 2006) (same).

c. Celgene's listing of the '358 Patent in the Orange Book is not evidence of an anticipatory disclosure.

Without any legal support, Defendants point to the fact that the '358 Patent includes broad genus claims that cover apremilast as a proxy for disclosure of apremilast in the '358 Patent. This is incorrect. Prior art patent claims to a genus of compounds do not negate a later patent to a specific compound that is covered by that earlier patent. *In re Rosuvastatin Calcium Pat. Litig.*, 719 F. Supp. 2d 388, 403–04 (D. Del. 2010), *aff'd*, 703 F.3d 511 (Fed. Cir. 2012) ("[T]he fact that a later invention may infringe an earlier patent does not affect the patentability of the later invention . . . ."). That is because a prior art disclosure of a broad class of compounds does not anticipate a later claim to a specific compound covered by that class if the prior art does not "expressly spell[] out a definite and limited class of compounds that enabled [the POSA] to at once envisage each member of this limited class." *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006); *see also Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006) (affirming finding of no anticipation where a prior art patent application disclosed a broad generic formula encompassing, but not specifically identifying, the claimed compound). Indeed, in the pursuit of drug discovery, an entirely new class of compounds

(a genus) may be invented and only through further research and development are subclasses or individual compounds (species) with unique or unexpected properties invented and patented. *See, e.g.*, *UCB*, 890 F.3d at 1321 (the prior art patent claimed a genus, which covered the asserted species, while the asserted patent claimed the asserted species specifically).

For the same reasons, Celgene's listing of the '358 Patent in the Orange Book for Otezla does not mean that the '358 Patent discloses stereomerically pure apremilast. Celgene was required to list in the Orange Book "each patent that claims the drug or a method of using the drug that is the subject of the NDA . . . with respect to which a claim of patent infringement could reasonably be asserted . . . ." 21 C.F.R. § 314.53; *see also* 21 U.S.C. § 355(b)(1) (same). Claim 1 of the '358 Patent covers apremilast—along with billions of other compounds. *See* PF ¶ 348.

Defendants' failure to show that stereomerically pure apremilast was disclosed by the '358 Patent is fatal to their anticipation argument.[3]

3. The '358 Patent Is Not an Enabling Prior Art Reference.

"A reference that is not enabling is not anticipating." *Forest Labs.*, 501 F.3d at 1268. Here, the '358 Patent cannot anticipate the asserted claims of the '638 and '536 Patents for the additional reason that the '358 Patent does not *enable* stereomerically pure apremilast. *Id.* (holding that a pharmacology paper that did not disclose how to obtain an enantiomer was not an anticipatory disclosure of the enantiomer). While a prior art patent is presumed to be enabled, that presumption is overcome by a showing that undue experimentation would be required to achieve enablement.

[3] Pursuant to the Court's order, ECF No. 465 at 2, 4 & n.1, neither the excluded evidence and stricken testimony of Dr. Gribble nor the withdrawn testimony of Mr. Mercer concerning Defendants' anticipation defense to the '638 Patent will be addressed. To the extent Defendants intend to advance a new theory based on European Patent 1752148 (EP '148) itself, they have not established how EP '148 is relevant to the '638 Patent. *Cf. In re Larsen*, 292 F.2d 531, 533 (C.C.P.A. 1961) ("We have repeatedly held that, in view of the differences between foreign patent laws and those of the United States, the allowance of patent claims in foreign countries is not pertinent to the question whether similar claims should be allowed here.").

Sanofi, 550 F.3d at 1085. The "*Wands*" factors are used to determine whether undue experimentation would have been required. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

a. Undue experimentation was required.

Dr. Davies's *Wands* analysis demonstrates that the '358 Patent would not have enabled the POSA to make stereomerically pure apremilast for use in a pharmaceutical composition without undue experimentation. PF ¶¶ 436–460. In contrast, Dr. Gribble did not consider whether the '358 Patent would have enabled the POSA to make stereomerically pure apremilast, nor did he conduct a *Wands* analysis. PF ¶¶ 434–435.

1. Whether the patent discloses specific working examples. Neither the '358 Patent nor any other reference published before March 2001[4] teaches a recipe for making apremilast. PF ¶¶ 356, 447. The '358 Patent also does not disclose any specific working examples to make any enantiomer of any compound. PF ¶¶ 343, 381–382.

2. The amount of guidance presented in the patent. The '358 Patent provides no guidance for preparing stereomerically pure apremilast. PF ¶¶ 353–354, 356, 448–450. The '358 Patent discloses a recipe for making Example 12, a racemate (PF ¶ 336), and lists three general routes, all known in the prior art, for trying to obtain enantiomers of Formula I: resolution by chiral chromatography, preparation in chiral form (or direct chiral synthesis), and resolution by chiral acid salt formation. PF ¶¶ 353, 381–383. But the patent does not disclose which—or whether ***any***—of these three general routes may be applied to Example 12, specifically, to obtain its enantiomers in any level of stereomeric purity. PF ¶¶ 354, 377–378, 387. In fact, the POSA would have been skeptical that this list applied to Example 12 at all because the POSA would have

[4] Whether a prior art patent is non-enabling is evaluated as of one year prior to the earliest filing date of the patents-in-suit—for the '638 and '536 Patents, one year prior to March 2002. *See Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001).

recognized that one of the general routes—chiral acid salt formation—would be inoperable given the structure of Example 12. PF ¶¶ 376, 386.

One of the other routes listed in the '358 Patent, chiral chromatography, would have been particularly challenging. PF ¶¶ 405–431. Far from being the "universal" technique Defendants assert, it involves multiple steps. *Id*. To successfully employ this technique for Example 12, the POSA first would have had to develop a small-scale, or "analytical scale," chiral chromatography method through trial-and-error experimentation, by selecting from an immeasurable combination of experimental conditions, including selecting the chiral stationary phase, solvent, pH, temperature, and flow rate, without guidance. *Id*. Even if the POSA had been successful in creating an analytical method, to acquire enough material for use in a pharmaceutical composition the POSA would then have had to repeat the trial-and-error development process at a larger, preparative scale, for which the analytical scale work may or may not be of assistance. PF ¶¶ 425–431. The POSA would have also expected that Example 12 may be particularly difficult to resolve by chiral chromatography because the compound may be unstable in the presence of acid, base, or polar solvents—all common elements of chiral chromatography experiments. PF ¶ 424.

Thus, the POSA seeking to make stereomerically pure apremilast would have been left to trial-and-error experimentation to hopefully achieve a successful direct chiral synthesis. PF ¶¶ 388–391. Since the literature provided no guidance, the POSA would have had to design a multi-step synthetic route from scratch, including selecting starting materials and reagents, solvents, and reaction conditions—a nearly infinite number of choices. *Id*. Such a route could take many months to develop, and if any one step in the route failed, the entire synthesis would have failed. PF ¶ 389 (explaining Dr. Davies' work on an 8-step synthesis).

3. The time and cost of any necessary experimentation. Any of the three general

routes listed in the '358 Patent would have required substantial time and cost to achieve stereomerically pure apremilast, if it was possible at all, because the POSA would have had to develop a specific method through trial-and-error experimentation. PF ¶¶ 384, 432, 436–441.

4. How routine any necessary experimentation is in the field. The amount of experimentation considered routine to prepare enantiomers would have been the small adjustments required to adapt or fill in any informational gaps to a published method to the particular equipment and resources available in a chemist's laboratory. PF ¶¶ 442–445. Developing a separation method or direct chiral synthesis entirely from scratch was not "routine" experimentation. PF *Id*.

5. The nature and predictability of the field. Preparation of enantiomers was highly unpredictable, and methods were developed through trial-and-error. PF ¶¶ 384, 387, 451–452.

6. The level of ordinary skill in the field. Even an expert would have had to resort to trial and error in trying to prepare a never-before prepared enantiomer. PF ¶¶ 453–458. For example, Dr. Davies explained that he formed a company in 1992, Oxford Asymmetry, which aimed to provide single enantiomer compounds to researchers precisely because this was a difficult task and not something that ordinary researchers would reasonably expect to achieve. PF ¶ 457. Because making single enantiomers was so difficult, Oxford Asymmetry would never promise results—even experts in making single enantiomers did not reasonably expect success in this area. *Id*. Indeed, Dr. Davies explained how his own research group at the University of Oxford tried to resolve a particular amine compound for nearly 20 years without any success. PF ¶ 458.

7. Nature and scope of the disclosure. The '358 Patent's disclosure pertains to the discovery of a large class of compounds with only general descriptors of properties that may be found amongst the billions of compounds. The general routes to obtain enantiomers merely restated the state of the art, providing nothing more than an invitation to experiment. PF ¶¶ 381–

383, 459–460.

The first six *Wands* factors above weigh decidedly in favor of undue experimentation. The seventh factor is neutral. Overall, the *Wands* factors demonstrate that undue experimentation would have been required to make stereomerically pure apremilast.

b. The inventors did not "admit" that making stereomerically pure apremilast was routine

Defendants seek to sidestep the proper analysis by pointing to a statement in the '638 Patent itself that they assert is an "admission" by the inventors that it would have been routine for the POSA to make stereomerically pure apremilast. *See* JTX-3 at 9:13–17. But this misconstrues the passage (Compound A referring to apremilast.):

> Compound A can be isolated from the racemic compound by techniques known in the art. Examples include, but are not limited to, the formation of chiral salts and the use of chiral or high performance liquid chromatography "HPLC" and the formation and crystallization of chiral salts. See, e.g., Jacques, J. et al., *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S.H., et al., *Tetrahedron* 33:2725 (1977); Eliel, E.I., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S.H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.I. Eliel, Ed. Univ. of Notre Dame Press, Notre Dame, Ind., 1972).

Id. at 9:13–24. This passage, appearing under the "Detailed Description of the Invention," says nothing about whether or how routine it would have been for a POSA to make apremilast in the absence of the specific method disclosed for the first time later in the '638 Patent. JTX-3 at 21:6–22-29. What is possible after the disclosure of a new invention is vastly different from what the POSA could obtain without undue experimentation before its disclosure. This passage at 9:13–24 lists two general techniques known in the art for isolating enantiomers from the racemic compound: the formation of chiral salts (listed twice) and the use of chiral chromatography. *Id.* This is a far cry from an "admission" that the POSA would have been able *to make stereomerically*

pure apremilast without undue experimentation using those techniques. As Dr. Davies explained, that techniques were known for isolating enantiomers in general is not the same as applying those techniques to a particular compound. PF ¶¶ 461–463; Trial Tr. at 1472:17-18 (Davies Direct 6.23.21) ("but finding those conditions, that's the trick."). As described above, Section I.A.3, finding the conditions to make enantiomers is a trial-and-error process.

The Court should find that Defendants have not met their heavy burden of demonstrating that the '358 Patent anticipates the asserted claims of the '638 and '536 Patents.

B. Defendants Have Not Proven by Clear and Convincing Evidence That the Asserted Claims of the '638 Composition Patent Would Have Been Obvious.

Neither of Defendants' two combinations—(1) the '358 Patent and WO '606 and (2) the '358 Patent and Takeuchi—render the asserted claims of the '638 Patent obvious.

Obviousness may not be shown by working backward from a claimed compound with the benefit of hindsight. *Amerigen Pharms. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019). But that is exactly what Defendants did in this case: Dr. Gribble, Defendants' expert, began his analysis not with a review of the prior art on PDE4 inhibitors, but by focusing on Celgene's '358 Patent as if it were the leading light on PDE4 inhibitors. It was not. Dr. Gribble started with it because it was provided to him by Defendants' counsel and then focused on one of the example compounds, Example 12, which is a racemate that shares the same structural connectivity as apremilast, an enantiomer, PF ¶¶ 226, 234, 305, 327. This is error. The Federal Circuit has adopted an analytical framework to stave off the insidious nature of hindsight bias that so often arises in new chemical compound cases such as this one. This framework requires a specific motivation to select a "lead compound" based on the compound's known properties, not on structural similarity to the claimed compound. Defendants argue against use of this framework; because the facts do not permit a conclusion of obviousness under it. The '358 Patent contains

nothing that would motivate the POSA to select it as a starting point for further development—it contains no biological data for any of the billions of compounds it covers. PF ¶¶ 315–317. There is no evidence that anyone other than Celgene thought that the compounds of the '358 Patent, all of which are thalidomide analogs, were promising compounds.

Defendants also attempt to disregard their failure to show a reason to start with the '358 Patent by conflating a broad genus patent that "covers" a universe of potential compounds (such as the billions of compounds claimed in claim 1 of the '358 Patent) and a narrow composition patent that discloses and claims one of the species within that genus (such as the claims to a pharmaceutical composition containing apremilast in the '638 Patent). But the disclosure of a genus in the prior art does not automatically make the species obvious. *See In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) (rejecting obviousness challenge based upon a prior art patent's disclosure of a generic formula encompassing millions of compounds because it did not "teach or fairly suggest the selection" of the claimed compound); *see also In re Rosuvastatin*, 719 F. Supp. 2d at 403–04. And when the Patent Office specifically examined the patentability of the asserted claims of the '638 Patent in view of the '358 Patent, it determined that the '358 Patent neither taught nor suggested modifications to obtain compositions of stereomerically pure apremilast and thus did not render the '638 Patent obvious. PF ¶¶ 306–307. *See Tokai Corp.*, 632 F.3d at 1367.

Other than through hindsight, Defendants cannot explain why the POSA would have turned to the '358 Patent, selected Example 12, made and tested its enantiomers, or reasonably expected apremilast's properties. Defendants' ancillary references, WO '606 and Takeuchi, do nothing to change that analysis.

1. The Asserted Claims of the '638 Composition Patent Are Entitled to a Priority Date of October 21, 1999.

Claims 3 and 6 of the '638 Patent are directed to pharmaceutical compositions suitable for

oral administration to a patient comprising stereomerically pure apremilast and a pharmaceutical acceptable carrier, excipient, or diluent. JTX-3 at cl. 1, 3, 6. Claim 6 further specifies that the amount of stereomerically pure apremilast is between 10 and 200 mg. *Id.* at cl. 6; *see also* PF ¶¶ 9–14. Because a patent claim is entitled to claim priority to the date of conception of the invention, so long as it is followed by a reasonable diligence in reducing to practice, the asserted claims of the '638 Patent are entitled to a priority date no later than October 21, 1999, when Dr. Hon-Wah Man synthesized stereomerically pure apremilast. PF ¶¶ 280–282. *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577 (Fed. Cir. 1996). By that time, the inventors had been synthesizing and testing SelCIDs (thalidomide analogs with both TNF and PDE4 inhibitory properties) since at least 1994, aiming to develop oral pharmaceutical compositions. PF ¶¶ 283–291. Accordingly, the inventors had a "'definite and permanent idea of the complete and operative invention'" and thus conception of the invention. *E.I. du Pont De Nemours & Co. v. Unifrax I LLC*, 921 F.3d 1060, 1075 (Fed. Cir. 2019) (quoting *Mahurkar*, 79 F.3d at 1577). Establishing an October 21, 1999 priority date does not change the scope and content of the prior art, but does bear on whether and how the '358 Patent could serve as a blocking patent for the '638 Patent for purposes of commercial success, discussed below at Section I.B.8.e.

"To establish an actual reduction to practice . . . 'the inventor must prove that: (1) he constructed an embodiment or performed a process that met all the limitations of the claim; and (2) he determined that the invention would work for its intended purpose.'" *E.I. du Pont De Nemours*, 921 F.3d at 1075 (citation omitted). The inventors diligently reduced their invention to practice by December 1999, subjecting stereomerically pure apremilast to a series of biological tests, including a murine shock model where apremilast was orally administered with water (a pharmaceutically acceptable excipient) to mice (which fall within the definition of a "patient") at

a dose of 1 mg/kg orally (the equivalent of 70 mg when administered to a human of average weight). PF ¶¶ 292–301. In that model, apremilast significantly reduced the inflammatory response in mice without causing significant toxicity. PF ¶¶ 240–47.

2. Defendants Failed to Prove That the POSA Would Have Selected Any of the '358 Patent Compounds as a Starting Point.

To avoid the insidious effect of hindsight, any obviousness analysis requires consideration of motivation: would the POSA have been motivated to start with and modify the prior art in a way that leads to the invention? *See KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 420 (2007). In a case involving a new chemical compound, the patent challenger must show the required motivation by demonstrating that: (1) "a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts"; and (2) "the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka*, 678 F.3d at 1291–92. Selection of a lead compound is not based on its structural similarity with the claimed compound. Rather, a lead compound is a "compound in the prior art that would be most promising to modify" and "a natural choice for further development efforts." *Id.* at 1292 (quotations omitted). "In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties." *Id.* Such properties include "positive attributes such as activity and potency," "adverse effects such as toxicity," and any other relevant characteristics known in the prior art. *Id.* This test reflects the realities of drug discovery: a POSA would not have had unlimited resources to make and test every prior art compound. PF ¶ 194.

It is undisputed that Defendants' experts did not perform a lead compound analysis. PF¶ 606. This alone is fatal to Defendants' obviousness case. Eschewing this analysis, Defendants

instead assert myriad starting points for their obviousness challenge (seventeen example compounds, Example 12, and apremilast[5]), all purportedly based on the '358 Patent. Dr. Gribble opined, in conclusory fashion, that the POSA, interested in finding a new PDE4 inhibitor, would have located the '358 Patent in his or her research. PF ¶ 607. But that is not the relevant inquiry. What Defendants are required to show is why the POSA would have ignored the plethora of PDE4 inhibitors with robust biological data available as of 1999, and focused instead on the compounds of the '358 Patent, which have no biological data. *See Daiichi Sankyo Co. v. Matrix Labs., Ltd*., 619 F.3d 1346, 1354 (Fed. Cir. 2010) (the patent challenger is "requir[ed] to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds ***over other compounds in the art***".) (emphasis added). Defendants candidly admitted that they did not even attempt to make such a showing, but instead simply started with the '358 Patent. PF ¶ 606.

a. The POSA would have chosen a lead compound with robust biological data as a starting point.

Had Defendants done the proper analysis and looked at all of the relevant prior art, as Dr. Knowles and Dr. Davies did (PF ¶¶ 492–576), a richer landscape of potential PDE4 inhibitors would have been revealed. By 1999, PDE4 as a therapeutic target had been intensively studied for more than a decade, and dozens of PDE4 inhibitors had been investigated in clinical studies and had published data about their biological properties. PF ¶¶ 512–19, 677. Among them, cilomilast and roflumilast, both in Phase 3 clinical studies, would have been natural choices as lead

[5] Defendants erroneously argue that the '358 Patent expressly discloses apremilast and then argue that if one had apremilast it would have been obvious to use it in a pharmaceutical compositions. As discussed above, (Section I.A.), the '358 Patent does not disclose apremilast or even teach how to make it, so it could not have been a starting point for the POSA. And the POSA would not have been motivated to locate it from the '358 Patent and use it in a pharmaceutical composition.

compounds. PF ¶¶ 553–68. Cilomilast was "the most significant PDE4 inhibitor" in development as of 1999, and was widely considered "the gold standard" against which all other PDE4 inhibitors should be compared. PF ¶¶ 559–60. In addition, at least eleven other PDE4 inhibitors, with disclosed structures, were in preclinical evaluations, or clinical studies. PF ¶¶ 569–73. Medicinal chemists would have selected among those compounds to start the iterative, data-driven process of identifying a new PDE4 inhibitor with the right combination of biological properties. PF ¶¶ 188–96, 539–52.

b. The POSA would have avoided thalidomide analogs.

In fact, the POSA would have had good reason to ***avoid*** the compounds of the '358 Patent. The '358 Patent exclusively involves thalidomide analogs, which would have raised concerns about the compounds' potential to cause fetal malformation or death, as well as other adverse events, like peripheral neuropathy. PF ¶¶ 580–90. While thalidomide was approved to treat complications of a potentially fatal form of leprosy in 1998, its prescribing information carried a four-page "black box warning"—the highest level of warning that FDA puts on an approved drug—for embryo-fetal toxicity. PF ¶¶ 524–26, 528–30. And as of 1999 or 2002, the POSA would not have known what aspect of thalidomide caused those effects or how to potentially overcome them. PF ¶ 533. As of 1999 or 2002, Celgene was the *only* company developing thalidomide analogs as PDE4 inhibitors. PF ¶ 587. In addition, the POSA would have also been concerned that the compounds of the '358 Patent may degrade into Michael acceptors under physiological conditions, as even parts per million of Michael acceptors can be carcinogenic. PF ¶ 590. Therefore, the '358 Patent, disclosing a broad genus that covered billions of thalidomide analogs without any biological data, would have been near the bottom of the barrel for the POSA seeking to develop a novel PDE4 inhibitor and no different than taking a stab in the dark.

Defendants have repeatedly suggested that by 1999 or 2002, the POSA would not have

been concerned about the potential toxicity of thalidomide analogs, because science had progressed and thalidomide analog development had been encouraged. To that end, Defendants pointed to several publications studying thalidomide analogs, and two thalidomide analogs (CDC-801 and CDC-998) that had gone into the clinic by 2002. PF ¶¶ 1109, 1113. Defendants ignored that these publications are largely authored or co-authored by scientists from Celgene, the small company developing both CDC-801 and CDC-998, and that these publications appropriately acknowledge the scant data and very strict controls over thalidomide itself. PF ¶¶ 215, 222, 1096, 1108, 1118. Indeed, as discussed below, FDA and sophisticated players in the industry like GSK were skeptical that thalidomide analogs could be successfully developed as PDE4 inhibitors without teratogenicity. *See* Section I.B.8.c.

The POSA would not have selected a thalidomide analog, like CDC-801 and CDC-998, as a lead compound given the availability of other options, like cilomilast and roflumilast, which had progressed further in the clinic—both were in Phase 3 clinical trials as of 1999 or 2002. In contrast, CDC-801 was in Phase 2 clinical trials. PF ¶¶ 570, 573. But even had the POSA selected CDC-801 as a lead compound, Defendants have adduced no evidence that the POSA would have been motivated to modify its structure to arrive at apremilast. PF ¶ 611. As to CDC-998, its structure was not publicly available by March 2002, so the POSA *could not* have selected it as a lead compound for further development.[6] PF ¶¶ 613–14. In any event, Defendants failed to provide any reason why the POSA would have selected any of the thalidomide analogs for which PDE4 potency or other data was reported in preference to cilomilast or roflumilast, or why the POSA would have been led by those other compounds to any of the compounds of the ’358 Patent,

[6] As of the priority date, the POSA would not have been able to associate CDC-998 with CC-7085 or with the ’358 Patent. As Dr. Schafer explained, Celgene used a different name in the public literature to protect the identify of compounds. PF ¶¶ 226–228.

including apremilast. PF ¶ 591. The '358 Patent, even among the undesirable compounds of thalidomide analogs, would not have been the POSA's choice as a lead or as the "most promising" starting point for further development.[7]

c. The POSA would not have chosen the seventeen example compounds of the '358 Patent as the starting point.

With the '358 Patent in hand, Defendants assert that the POSA would have chosen the seventeen example compounds, synthesized all of them (and optionally their thirty-four enantiomers), tested them, and somehow arrived at stereomerically pure apremilast. PF ¶ 609. But this is not a viable obviousness theory. It is an admission that the '358 Patent provides no lead compound and proves the non-obviousness of the claimed inventions. In fact, both sides' experts agreed that (1) *data* would have guided the POSA to identify the lead compound, and (2) the '358 Patent has *absolutely no biological data* for any of its billions of compounds, including its seventeen example racemates. PF ¶¶ 190–95, 315, 544–551. Without biological data, there would have been no reason for the POSA to select any compound from the '358 Patent and Defendants' expert provided none.

Instead of data, Defendants argue that the POSA would have taken as true all of the general statements in the '358 Patent, and understood that the example compounds represented the intentional choice by the inventors to illustrate compounds of particular interest, and that they are all useful as PDE4 inhibitors. But this is what the '358 Patent actually says:

> The compounds of the present invention are useful in the inhibition of phosphodiesterases, particularly PDE III and PDE IV, and in the treatment of disease state mediated thereby. . . .
>
> Decreasing TNFα levels, increasing cAMP levels and inhibiting

[7] Defendants have adduced no evidence that the POSA would reasonably have expected that the modifications to transform these thalidomide analogs into apremilast would result in a successful PDE4 inhibitor that possessed the beneficial properties of apremilast. PF ¶¶ 611–614.

> PDE4 thus constitute valuable therapeutic strategies for the treatment of many inflammatory . . . diseases.

DTX-174 at 4:28–38; PF ¶ 318. At most, the general statements from the '358 Patent would have told the POSA that the '358 Patent includes within its broad class of compounds *some* that are PDE4 or TNF inhibitors. PF ¶¶ 319–23. As Dr. Knowles testified, it would have been "mad" to read the '358 Patent as claiming that *all* the billions of compounds covered by Formula I inhibit PDE4 or TNF. Trial Tr. at 1736:9–1737:6 (Knowles Cross 6.25.21). Defendants' expert Dr. Gribble concurred. Trial Tr. at 654:16–22 (Gribble Cross 6.18.21) (observing that it is "highly unlikely" that every one of the billions of compounds within Formula I inhibited PDE4 and TNF); *see also* PF ¶¶ 319–323.

Defendants lack any scientific reason why the POSA would have found the seventeen example compounds of the '358 Patent to be promising drug candidates. According to the patent, there is nothing special about them; they are not "preferred" compounds, but serve only to "typify" the nature of the invention. PF ¶ 312. Given the complete lack of biological data, the POSA would have had no idea whether any of the example compounds inhibit PDE4 versus other phosphodiesterases, and, if so, whether they are selective for PDE4 and sufficiently potent to be suitable for use in a pharmaceutical composition. PF ¶¶ 313–314, 319–326. *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd*., 492 F.3d 1350, 1357–58 (Fed. Cir. 2007) (rejecting defendant's asserted lead compound in the prior art patent because (1) it was one of hundreds of millions; (2) no test data was provided; and (3) even though it was included as one of the fifty-four exemplary compounds, the prior art patent and its file history (which did provide data on nine compounds, including the asserted lead) provided no suggestion that it was among the most therapeutically beneficial or promising compounds).

d. The POSA would not have chosen Example 12 as the starting point.

Having failed to articulate a reason to select Example 12, Defendants instead argue that the POSA would have landed on Example 12 because, when the inventors did their research, initial potency testing found it to be the most potent among the seventeen examples in inhibiting TNF and among the most potent in inhibiting PDE4 (as confirmed by non-public Celgene data). As an initial matter, this argument is plainly hindsight-driven. Defendants, having access through discovery to the confidential Celgene data unavailable to the POSA at the time, are using it to direct the obviousness analysis. Moreover, Defendants' singular focus on TNF inhibition ignores what would have motivated the POSA in developing a PDE4 inhibitor.

First, the POSA would not have focused on potency, let alone TNF inhibitory potency, alone; instead, testing and evaluation of different biological properties would have been necessary. PF ¶ 599. *Second*, contrary to Defendants' assertion, Dr. Gribble testified that the POSA would have been motivated to find a compound that inhibited *PDE4*—not TNF. PF ¶ 603. Dr. Gribble's testimony accurately reflected the state of the art at the time of the invention: as Dr. Schafer testified, most companies developing PDE4 inhibitors at that time, unlike Celgene, did ***not*** focus on TNF. PF ¶¶ 208–210. *Third*, the difference between Example 12 and many other compounds in terms of TNF inhibition (as well as PDE4 inhibition) is minimal and could not have led the POSA, in any event, to have selected Example 12 over at least compounds 7, 10, and 16. PF ¶¶ 600–03. Therefore, it would not have been an obvious choice for the POSA to pick Example 12, even if the POSA had synthesized and tested all seventeen example compounds. PF ¶ 600.

3. The POSA Would Not Have Been Motivated to Prepare the Enantiomers of All of the Example Compounds of the '358 Patent, Let Alone Specifically of Example 12.

Preparation of single enantiomers is difficult, time consuming, and expensive. PF ¶¶ 380–

460. With limited time and resources, and no data to suggest that the seventeen racemates showed sufficient potency, the POSA would not have been motivated to make the thirty-four enantiomers of all seventeen example compounds, if that were even possible. PF ¶¶ 604–605.

With no data-driven motivation to prepare individual enantiomers of the example compounds, Defendants make the remarkable claim that "there was never a motivation not to separate enantiomers of a racemate." Trial Tr. at 604:18–605:3 (Gribble Direct 6.18.21). This grossly mischaracterizes the reality of drug discovery at the time of the invention, and is based on Defendants' misreading of the available literature. PF ¶¶ 624–33. Whether to prepare single enantiomers of a given racemate would have been decided on a case-by-case basis. *Id*. And in this case, there is no evidence that the POSA would have been motivated to separate the seventeen example racemic compounds of the '358 Patent. *Firs*t, there was no data to support the idea that the POSA would have reasonably expected these seventeen compounds to have sufficient potency meriting the time and expense of separating the enantiomers. PF ¶¶ 604, 634. *Second*, nor would the POSA have expected that the biological properties of the enantiomers would be any different from the example racemates, given Celgene's public focus on racemates. PF ¶¶ 635. The '358 Patent only discloses racemates. PF ¶ 310. CDC-801, the only SelCID reported to be in Phase 2 clinical studies by 1999, was a racemate developed by Celgene. PF ¶ 641. Furthermore, the ***only*** enantiomer data reported for any SelCID at the time suggested that the enantiomers were not more potent than their racemates. PF ¶¶ 636–640.[8]

Defendants suggest that the POSA would have been motivated to obtain the enantiomers

[8] Although unknown to the POSA, Celgene favored racemates. In addition to CDC-801, Celgene advanced CC-7085 (the racemate disclosed in Example 12 of the '358 Patent) into the clinic, ***after*** having succeeded in making apremilast and having discovered that apremilast had superior biological properties. PF ¶¶ 642–43.

of Example 12 because doing so may have avoided the potential teratogenicity of thalidomide and its analogs. But the converse is also true: obtaining the enantiomers may not have avoided the potential teratogenicity. Defendants' supposition ignores that as of 1999 or 2002, the thalidomide toxicity mechanism of action was unknown. So, the proposition that such a separation would avoid that toxicity would have been pure speculation, especially if apremilast, like thalidomide, were to racemize when it entered the human body. PF ¶¶ 533, 835–36. Even today, the actual mechanism by which thalidomide causes birth defects is not fully understood. PF ¶ 534. Moreover, the scientific literature then available suggested that separating the teratogenicity from the desired properties of a thalidomide analog could not be achieved by obtaining the "right" enantiomer, because both biological effects reside in a single enantiomer. PF ¶¶ 657–58.

4. Under *Aventis*, the POSA Would Not Have Had a Reasonable Expectation That Example 12 Had Any Desirable Properties That Resided in the S-Enantiomer.

Instead of the lead compound analysis, Defendants rely on the so-called "general obviousness analysis," without ever articulating what that is. If Defendants argue that such a "general obviousness analysis" is incompatible with the lead compound analysis framework, this argument is without merit. The Federal Circuit has held repeatedly that the lead compound analysis fits well within the obviousness framework set out by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), and ***is*** the general obviousness analysis applicable in the new chemical compound context. *See Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., Inc.*, 933 F.3d 1367, 1375 (Fed. Cir. 2019) ("[I]t ***remains necessary*** to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added); *Daiichi*, 619 F.3d at 1352; *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). Courts in this district have

followed the same framework.[9] Defendants also suggest that the lead compound analysis is limited to cases involving chemical modification, and in this case, there is none. But both sides' experts agreed that a racemate and its enantiomers are distinct chemical entities, PF ¶ 177, and changing one compound to another is chemical modification. PF ¶¶ 616–23.

Defendants assert that the guidance provided by *Aventis Pharma Deutschland GmbH v. Lupin, Ltd*., 499 F.3d 1293 (Fed. Cir. 2007) should be applied. But even under this guidance, Defendants cannot prevail because there simply is no biological data associated with any unique chemical structure in the '358 Patent or Example 12. PF ¶ 315. And, there is no information in the '358 Patent, or anywhere else in the prior art, that would have caused the POSA to believe that the (+) enantiomer of Example 12 had any beneficial properties over the racemate. PF ¶¶ 635, 655–656. The facts presented here are distinguishable from those of *Aventis*, which held that the claimed stereoisomer was obvious in light of the prior art's disclosure of (1) a prior-art, FDA-approved drug with a similar structure and a compound that was a mixture comprising the claimed stereoisomer, (2) ***known*** desirable properties associated with that compound (and with the FDA-approved drug), and (3) ***knowledge*** that the desirable properties were specifically associated with the claimed stereoisomer. 499 F.3d at 1300–03. In other words, *Aventis* applied a "lead compound" analysis: the prior art compound had known desirable properties, and the prior art provided a motivation to modify the prior art compound because those known desirable properties were understood to reside in a single stereoisomer. *Id.* at 1302. This knowledge would have motivated

[9] *See Pfizer Inc. v. IVAX Pharms., Inc.*, No. 07CV00174, 2010 WL 339042, at *7 (D.N.J. Jan. 20, 2010) (quoting *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356–57 (Fed. Cir. 2007)); *Shire LLC v. Amneal Pharms., LLC*, No. 11-3781, 2014 WL 2861430, at *17–18 (D.N.J. June 23, 2014), *aff'd in relevant part*, 802 F.3d 1301 (Fed. Cir. 2015) ("[T]he obviousness analysis ***must*** begin at the beginning, before the active was known, which is what the 'lead compound' analysis does.") (emphasis added).

the POSA to select and modify the prior art compound, just like in any lead compound case. *Id*. at 1301 ("[I]f it is ***known*** that ***some desirable property of a mixture*** derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with reason to believe that this is so, the purified compound is prima facie obvious over the mixture." (emphases added)). But here, given the absence of any biological data, the POSA would have had no reason to conclude that Example 12 (or any compound of the '358 Patent) possessed any desirable property that was attributable to only one of its enantiomers.[10] PF ¶¶ 635, 655–56.

Defendants suggest that the POSA would have been lead to the S-enantiomer of Example 12 because certain prior art references (*e.g.*, Muller 1999, Wnendt, and Takeuchi) disclose that the S-enantiomers of ***some*** thalidomide analogs were more active than the R-enantiomers in TNF assays. That argument is contrary to science. Even Dr. Gribble disagreed, noting that "there's no way to know in advance" which enantiomer of Example 12 is more potent and he has not seen anything in the prior art suggesting that the S-enantiomer of Example 12 had any desirable property over Example 12. Trial Tr. at 605:4–9 (Gribble Direct 6.18.21); PF ¶ 656. As Dr. Davies explained, Muller 1999, Wnendt, and Takeuchi disclose thalidomide analogs that are structurally different from Example 12. PF ¶ 661. There is no suggestion that any of them are PDE4 inhibitors. Indeed, the particular compound Defendants relied on in Muller 1999 was found to be inactive against PDE4. PF ¶ 659. Nothing in the prior art would have led the POSA to reasonably expect that the S-enantiomer of Example 12 would have desirable properties over the R-enantiomer, Example 12, or any of the other example racemates of the '358 Patent.

[10] Defendants' reliance on *Novartis Pharms. Corp. v. West-Ward Pharms., Int'l Ltd*., 923 F.3d 1051 (Fed. Cir. 2019) is also inapposite. *Novartis* addresses the obviousness of a method of treatment claim using a compound that was ***explicitly disclosed*** in the prior art. *Id*. at 1057. In contrast, apremilast was not disclosed in the '358 Patent, or any other prior art reference.

5. The POSA Would Not Have Had a Reasonable Expectation of Successfully Making Apremilast.

Even if the POSA had been motivated to make apremilast (they would not have been), the POSA would not have had a reasonable expectation of success in doing so. No prior art reference disclosed a recipe for preparing apremilast. PF ¶¶ 356, 447. In addition, no prior art references disclosed a recipe for preparing structurally similar compounds to apremilast. PF ¶ 433. Without guidance, the POSA would have had to develop a recipe from scratch, using trial-and-error. PF ¶ 384. As a general matter, making single enantiomers was a difficult, unpredictable, and time-consuming process. PF ¶ 632; *see supra* Section I.B.2. Courts have also recognized the difficulties associated with preparing enantiomers.[11] Defendants have not pointed to any teaching that would have provided a reasonable expectation of success in achieving apremilast.

Ignoring the difficulty in making even one enantiomer, Defendants asserted that the POSA would have synthesized and tested all of the seventeen racemates and their enantiomers—*fifty-one* compounds in total—to eventually arrive at apremilast. But this undertaking would have been a full-scale research program—not the "routine" process described by Defendants. PF ¶ 605. The POSA would have had to acquire a sufficient amount of each of the fifty-one compounds to test for the relevant properties that made a compound suitable for use in a pharmaceutical composition, test, and then analyze the data. *Id*. Such a process would have been time-consuming and expensive, while the POSA would have limited resources. PF ¶¶ 194, 605.

[11] *See, e.g., Forest Labs., Inc. v. Ivax Pharms., Inc*., 501 F.3d 1263, 1269–70 (Fed. Cir. 2007) (failure to separate racemate without undue experimentation supported non-obviousness); *see also Grunenthal GMBH v. Alkem Labs. Ltd*., 919 F.3d 1333, 1342 (Fed. Cir. 2019) ("[T]o have a reasonable expectation of success, one must be motivated to do more than merely vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.") (quotations omitted).

6. The POSA Would Not Have Had a Reasonable Expectation of Obtaining a Compound with Apremilast's Unique Properties.

The success of the claimed invention lies not just in having made a stereomerically pure compound, but in having made a stereomerically pure compound with the combination of desirable properties, including potency, selectivity, tolerability, safety, and drug-like properties, that allow it to be used in an oral pharmaceutical composition. *See, e.g.*, *Yamanouchi Pharm. Co. Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) ("[T]he success was finding a compound that had high activity, few side effects, and lacked toxicity."). Given the absence of biological data on the '358 Patent compounds, the POSA would not have reasonably expected any desirable properties in any of the '358 Patent's compounds, let alone apremilast. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) ("[T]here is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.").

Here, as it turns out, apremilast has exceeded expectations in every aspect. As explained below (Section I.B.8.d), apremilast had a combination of properties that would have been a rarity among PDE4 inhibitors as of the priority date, lacked the teratogenicity and toxicity associated with thalidomide, and did not degrade to form a Michael acceptor under biological conditions. PF ¶¶ 654, 805. These data further confirm non-obviousness. *See, e.g.*, *In re May*, 574 F.2d at 1095 (finding establishment of "a substantial record of unpredictability vis-à-vis a highly significant combination of properties"); *Sanofi*, 550 F.3d at 1089 (holding the enantiomer non-obvious based on its "unexpected and unpredictable properties"). Even under Defendants' erroneous legal framework, apremilast's unexpected properties would rebut any *prima facie* case of obviousness.

7. Neither WO '606 nor Takeuchi Can Remedy the Deficiencies in Defendants' Obviousness Argument

Defendants' secondary references, WO '606 and Takeuchi, remedy none of the

deficiencies of the '358 Patent, and, in the case of WO '606, suggest that compounds with the structure of Example 12 are not preferred.

WO '606 is a later-filed Celgene application that, like the '358 Patent, discloses billions of thalidomide analogs. PF ¶¶ 472, 475. Also similar to the '358 Patent, WO '606 contains no biological data, and provides the same general guidance on enantiomer preparation. PF ¶¶ 475, 479. While there is overlap between the compounds of WO '606 and the '358 Patent, and Example 12 is within the scope of both Formulae I, WO '606 in combination with the '358 Patent teaches ***away*** from Example 12, explaining that certain compounds (of which Example 12 is one) are ***not*** preferred. PF ¶¶ 482. Example 12 is not mentioned in any of the seventy-eight examples of WO '606 (either as an example compound or exemplified pharmaceutical formulation). PF ¶ 478. Accordingly, there would have been no motivation to acquire an enantiomer of Example 12, even if WO '606 were read to suggest that the compounds of that application are preferentially administered as a single enantiomer. PF ¶¶ 666–68.

Takeuchi comes from an academic group studying a "close structural mimic" of thalidomide. PF ¶¶ 483–84. It does not discuss any compound of the '358 Patent, and provides no information on PDE4 inhibition. PF ¶¶ 485, 488. While Takeuchi reports that the S-enantiomer of 3-fluorothalidomide appeared to be more active than the R-enantiomer, Takeuchi notes that the result was not statistically significant and further studies were needed. PF ¶ 489. Takeuchi teaches the POSA nothing about how to prepare apremilast, as the analytical chromatography method used was limited to the particular compound studied and did not produce amounts sufficient for biological testing. PF ¶¶ 491, 670. Finally, Takeuchi would not have addressed the POSA's concern regarding teratogenicity of thalidomide analogs, because it did not assess this toxicity. PF ¶ 491. Therefore, the POSA would not have been motivated to combine the '358 Patent with

Takeuchi and arrived at apremilast, with a reasonable expectation of success. PF ¶¶ 669–72.

8. Objective Indicia Further Demonstrate the Non-Obviousness of the Asserted Claims of the '638 Composition Patent and the '536 Psoriasis Patent.[12]

Objective indicia, "[w]hen present . . . may often be the most probative and cogent evidence [of non-obviousness] in the record." *Procter & Gamble*, 566 F.3d at 998 (quotation omitted); *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012) ("[A] fact finder in district court litigation may not defer examination of the objective considerations until after the fact finder makes an obviousness finding[.]").

a. That others in the field tried and failed to develop a PDE4 inhibitor is strong evidence of non-obviousness.

"[E]vidence of failed attempts by others could be determinative on the issue of obviousness." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000) (collecting cases). The purpose of this evidence "is to show 'indirectly the presence of a significant defect in the prior art, while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan.'" *In re Cyclobenzaprine*, 676 F.3d at 1082 (citation omitted).

Since the discovery of PDE4 in the late 1980s, the pharmaceutical industry sought to develop a PDE4 inhibitor suitable for use as a pharmaceutical compound. PF ¶¶ 493, 512, 730. By October 1999 and March 2002, many, if not most, pharmaceutical companies were seeking to capitalize on PDE4 inhibitor's well-known anti-inflammatory properties to develop a safer and more tolerable therapy. PF ¶¶ 513, 684, 730. By 1999 and 2002, hundreds of PDE4 inhibiting compounds were reported in the literature; however, these compounds rarely advanced to clinical trials, and none had received FDA approval. PF ¶¶ 677–724. Many of these compounds were

[12] The non-obviousness of the '536 Patent is discussed further below.

reported to have been discontinued—failed—because of shortcomings in efficacy or tolerability. PF ¶¶ 680–81; *see also* ¶¶ 677–724. Even where no specific reason was reported, the fact that a compound was discontinued suggests the compound was not suitable for use as a pharmaceutical: companies would sell, or attempt to sell, a valuable asset if their priorities had changed. PF ¶¶ 682, 700–05. Even today, roflumilast, the only other FDA-approved oral PDE4 inhibitor, is approved for a narrow subset of COPD patients, and has tolerability issues. PF ¶¶ 706, 722–24.

Unable to deny that scores of other PDE4 inhibitors were discontinued, Defendants urge the Court to discount the evidence for a host of reasons. Defendants (1) posit that PDE4 inhibitors may have been discontinued for reasons unrelated to product shortcomings; (2) argue that post-invention date failures (or knowledge of the failures) cannot be probative of non-obviousness; (3) attribute the failures to *inhaled* rather than *oral* routes of administration; and (4) assert that failures of other PDE4 inhibitors are of no import because they do not concern failures to try and make apremilast, specifically. These arguments misrepresent the evidence or misstate the law.

First, Defendants have no example of even one PDE4 inhibitor that failed for reasons unrelated to shortcomings in the drug compound. While Dr. Page asserted that V11294A was discontinued for reasons unrelated to such shortcomings, he admitted that he did not confirm that was the case with the owners of the company and that the literature reported that V11294A was discontinued because of poor efficacy. PF ¶¶ 702–03.[13] In any event, to posit that the scores of PDE4 inhibitor candidates were discontinued for reasons unrelated to the compound's properties

[13] Dr. Page mentioned one other compound that purportedly was discontinued because of reasons unrelated to its shortcomings. That evidence was excluded. ECF. No. 465 at 5–6. On cross-examination, Dr. Page alluded to another compound as one he understood had been discontinued for reasons unrelated to shortcomings in the compound. Presumably he did not refer to that other compound, CDP840, by name because the literature reported that it was discontinued because of "disappointing efficacy." *See* ECF No. 454 at n.2; PF ¶¶ 704–05.

beggars belief: pharmaceutical companies are highly unlikely to simply choose to discontinue a product that is otherwise proving to be successful. PF ¶¶ 682, 700–05.

Second, that a failure post-dates the invention does not mean it is not probative of non-obviousness. *See, e.g.*, *Abraxis BioScience v. Actavis LLC*, Civ. No. 16-1925 (JMV), 2017 WL 9808442 (D.N.J. Sept. 12, 2017) at *2–3 ("product development documents, before and after the issue date of Plaintiff's patents, are relevant to the failure of others"); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, No. 09–MD–2118, 2010 WL 3766530, at *1-2 (D. Del. Sept. 21, 2010) (("[b]ecause science necessarily builds upon past discoveries, failure of others after a patent's issue date may be more persuasive than failures that occur before.").

Third, while Dr. Page attempted to dismiss some of the failures because they concerned inhaled (rather than oral) products, the literature reported that the inhaled route was considered a route of delivery that could, compared to oral administration, potentially avoid the systemic side effects that had plagued PDE4 inhibitors. PF ¶¶ 738–39. Thus, failures of *inhaled* PDE4 inhibitors are highly relevant in showing the difficulty in arriving at a suitable *oral* PDE4 inhibitor.

Fourth, Defendants are simply wrong to wave aside all of the failures with other PDE4 inhibitors. It is not necessary to show that others failed to create the patented invention, but only that the "alleged failure must be directed *to the problem that a patent purports to solve*." *In re Cyclobenzaprine*, 676 F.3d at 1082 (emphasis added); *Alco Standard Corp v. Tenn. Valley Auth.*, 808 F. 2d 1490, 1500 (Fed. Cir. 1986) ("Westinghouse, a large corporation working on this matter, had tried but failed [to solve the problem]. Indeed, Westinghouse had pursued other solutions to the problem, using [other technologies]."); *Teva Neuroscience, Inc. v. Watson Labs., Inc.*, Civ. No. 10-5078, 2013 WL 12318005, at *22 (D.N.J. Sept. 20, 2013) (failure of others to develop compounds to treat Parkinson's disease supported non-obviousness of patented compound that

succeeded as a Parkinson's disease treatment). Here, the problem that the others failed to solve was finding a PDE4 inhibitor with sufficient anti-inflammatory activity that could avoid side effects including nausea and emesis. PF ¶¶ 725–28. Each and every compound that failed to solve this problem is therefore a failure of others to develop a PDE4 inhibitor. The evidence of dozens of failed PDE4 inhibitors is highly probative of non-obviousness.

b. The existence of a long-felt, unmet need supports the non-obviousness of the claimed inventions.

"Evidence [of a long-felt need] is particularly probative . . . when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *In re Cyclobenzaprine*, 676 F.3d at 1082. Apremilast and Otezla met multiple long-felt needs that existed in October of 1999 and March 2002.

(1) Otezla met the long-felt need for a PDE4 inhibitor suitable for use as a pharmaceutical composition.

As discussed above in Section I.B.8.a, the pharmaceutical industry recognized the need for a PDE4-inhibiting treatment in the 1980s, and attempted to develop such a compound. Despite these efforts, the need remained unmet in October 1999 and in March 2002. PF ¶¶ 729–50. Apremilast succeeded where other PDE4 inhibitors failed, and has filled a substantial need for patients who have psoriasis, psoriatic arthritis, and Behcet's disease. PF ¶¶ 744–46. That the inventors of apremilast found a solution that eluded sophisticated well-resourced pharmaceutical companies for years further demonstrates the non-obviousness of the inventions.

A nexus exists between the evidence of this long felt-need and the asserted claims of the '638 Patent because they claim a pharmaceutical composition comprising stereomerically pure apremilast. Similarly, a nexus exists between this evidence and the asserted claim of the '536 Patent because the asserted claim of the '536 Patent claims a method of treating psoriasis by administering stereomerically pure apremilast. PF ¶¶ 751–53.

(2) Otezla met the long-felt need for a safer, effective oral psoriasis treatment without barriers to adherence.

(a) The prior art treatments failed to meet the need.

The three categories of drugs used to treat psoriasis before Otezla became available were topical treatments, older oral systemics, and biologics. PF ¶¶ 765. Due to drawbacks associated with each category of treatments, as of October 1999 and March 2002 (PF ¶¶ 766–96), a significant patient population with plaque psoriasis was forced to choose between treatments that were ineffective for their disease state and treatments that presented serious safety concerns and burdens to initiating and adhering to therapy. PF ¶ 797. As a result, undertreatment of psoriasis was common, and there was an unmet need for a safer treatment, that was effective, and did not have the barriers to adherence present in existing treatments. PF ¶ 797.

Topicals were not a viable treatment option for moderate-to-severe plaque psoriasis and were associated with a number of drawbacks including limited efficacy, especially for chronic use; time-consuming application; and challenges created by the left-behind sticky or greasy residue. PF ¶¶ 766–70. The prior art oral systemic treatments—methotrexate, acitretin and cyclosporine—offered better efficacy than the topicals but were associated with serious safety risks, which also caused burdens such as monitoring and testing for potential organ damage. PF ¶¶ 771–87.

As of March 1999 and 2002, none of the biologic treatments now available for psoriasis had received FDA approval for psoriasis. PF ¶ 789. When those biologics later became available, they failed to meet the needs of many patients who wanted a psoriasis treatment that did not carry serious safety risks including serious infections and malignancies or who found injectable or intravenous routes of administration and cold-storage requirements burdensome. PF ¶¶ 788–96.

Defendants' dermatology expert, Dr. Gilmore, admitted that as of 2012, a need existed for a safer, more effective, and more convenient drug for treating patients suffering from psoriasis,

and that a significant gap existed as late as 2013 in the prior art treatments that disadvantaged many patients—all years after a number of biologics had been approved to treat plaque psoriasis. PF ¶ 798. In other words, Dr. Gilmore admitted that the unmet need persisted despite the availability of the three categories of drugs used to treat psoriasis before Otezla became available. And Defendants' attempts to minimize Otezla's impact by treating each attribute of a drug in isolation, e.g., by just comparing biologics' efficacy to that of Otezla, ignore the reality that the POSA faced: patients and prescribers must consider each therapeutic option as a whole with all of its associated benefits and risks when determining which drug is best for each patient given all of the patient's individual factors such as needs and treatment goals. PF ¶ 801.

(a) Otezla filled the articulated need.

By providing patients with a treatment that offered better efficacy than topicals, without the serious safety risks and burdens to adherence associated with other oral systemics and biologics, Otezla filled the needs of patients who were inadequately treated by prior art therapies and who had reluctantly accepted greater safety risks than necessary. PF ¶¶ 799–809. Even Defendants' expert, Dr. Gilmore, agreed with a 2012 statement that apremilast's overall features positioned it to fill a gap in the management of psoriasis. PF ¶ 800.

Otezla has a pristine safety profile and carries no black-box warnings. PF ¶¶ 803–05. To obscure this, Defendants improperly conflated Otezla's GI side effects (which typically resolve after the initial weeks of treatment) and Otezla's very rare incidences of depression, with the potentially fatal side-effects of oral systemic and biologic treatments, including bone marrow toxicity, organ damage, and cancer. PF ¶¶ 773–780, 794, 806. In physician surveys, Otezla received higher marks for long-term safety than biologics, and vastly outperformed methotrexate on that metric. PF ¶¶ 956–58. Dermatologists identified Otezla's safety profile as one of the primary reasons they prescribe the drug. PF ¶¶ 956–57.

At the same time, Otezla also offers better long-term efficacy than topicals, allowing many patients to achieve significant skin clearance and improved quality of life. PF ¶¶ 937–42. Defendants emphasize that biologics can clear skin better than Otezla, but ignore that maximum skin clearance may not be the patient's foremost goal, and that there are many patients for whom Otezla's combination of superior safety, efficacy, and lack of treatment barriers strikes the right balance. PF ¶¶ 801, 937–42.

As an oral therapy with no required lab monitoring, Otezla allows many patients to reach their treatment goals without the barriers to adherence present with messy topicals, oral systemics that require lab monitoring or abstention for alcohol, or biologics that must be administered using a needle and stored in temperature controlled conditions. PF ¶¶ 935–37. Physician surveys confirmed Otezla satisfied this element of the need, and consistently indicated that Otezla's lack of lab monitoring and oral route of administration are reasons for prescribing the drug. PF ¶¶ 954–57. Dr. Gilmore attempted to downplay the extent to which injectable or intravenous administration presented a burden to psoriasis patients by focusing on the auto-injection pen devices utilized today, which ignores that biologics were injected by traditional syringes during much of the relevant time period. PF ¶¶ 792–93.

A nexus exists between the unmet need and the asserted claims. As an initial matter, a nexus is presumed between Otezla's clinical and commercial success and the asserted claims because Otezla embodies the claims. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016); PF ¶¶ 66–67. Moreover, Otezla has met the need for an improved treatment for psoriasis because of its therapeutic properties—namely its safety, its efficacy, its oral route of administration, and its unique PDE4 mechanism of action, all of which are attributable to Otezla's active ingredient, stereomerically pure apremilast, and the method of treating psoriasis by

administering stereomerically pure apremilast, as claimed in the '638 and '536 Patents respectively. PF ¶¶ 810–12. Defendants are incorrect that such a nexus exists only if the elements of the need are explicitly described in the asserted claims. *Immunex Corp. v. Sandoz Inc.*, 395 F. Supp. 3d 366, 405–06 (D.N.J. 2019) (nexus between patents claiming the active ingredient for Enbrel and methods for manufacturing the compound, and Enbrel's ability to meet a "long-felt need for an effective, wide-reaching rheumatoid arthritis drug" although none of the asserted claims require that the compound be "effective" or "wide-reaching"), *aff'd*, 964 F.3d 1049 (Fed. Cir. 2020); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013) (improper to reject evidence related to need for high-speed memory systems simply because asserted claims did not recite a specific clock speed; evidence was reasonably commensurate with the scope of the claims because the claimed features enabled high-speed transfer of data).

c. Industry skepticism supports non-obviousness.

"If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness." *WBIP*, 829 F.3d at 1335. Thalidomide is a notorious teratogen responsible for the biggest pharmaceutical disaster in history, resulting in birth defects in tens of thousands of babies and innumerable miscarriages and stillbirths. PF¶¶ 520–23. Decades after the disaster, in 1998, thalidomide had been reintroduced to the market to treat aspects of ENL, a form of leprosy with no other treatment options, under highly regulated conditions. PF¶¶ 524–31. Critically, as of 1999-2002, the mechanism by which thalidomide caused teratogenicity was unknown; and it was not fully understood which part (or parts) of the compound were responsible. PF ¶¶ 533–34.

Against this backdrop, apremilast's structural similarities with thalidomide (both share a thalimido ring) were cause for skepticism from FDA and other companies in the industry, especially given Celgene's plans to use apremilast to treat psoriasis, a disease that was not as

serious or life threatening as leprosy and for which other treatments were available, albeit with their own limitations. PF ¶¶ 814–69. In responding to Celgene's IND for apremilast, FDA provided a list of safety concerns about apremilast's relationship with thalidomide. PF ¶¶ 823–47. In particular, the chemist responsible for reviewing the apremilast IND at FDA wanted additional reassurances and information regarding apremilast's relationship to thalidomide, including information on whether apremilast might racemize in the body. PF ¶¶ 835–43. These are exactly the questions that the POSA—who both sides agree is a chemist—would have had and show why the POSA would have avoided the compounds of the '358 Patent, including Example 12.

Defendants attempted to downplay this clear evidence of FDA skepticism by superficially noting that FDA does not use the word "skepticism" in its communication. PF ¶ 847. But FDA used the word "concerns"—relaying the skepticism that the FDA chemist raised about whether apremilast would be safe to use in humans. PF ¶¶ 823–47. Even after Celgene responded to FDA's concerns and provided FDA with additional data, FDA instructed Celgene to require women of childbearing age in the clinical trials to use two forms of birth control. PF ¶¶ 841–46. Indeed, only men and surgically sterile or post-menopausal women were subjects in the Phase 1 apremilast studies. PF ¶¶ 820–21.

GlaxoSmithKline ("GSK"), approached by Celgene as a potential licensing partner and which entered into a research collaboration with Celgene, also demonstrated skepticism towards apremilast. PF ¶¶ 856–69. Dr. Knowles, who was involved with GSK's evaluation of apremilast, testified that although apremilast had highly promising properties, GSK ultimately declined to license apremilast over concerns raised by other GSK scientists and GSK's commercial team about apremilast's relationship with thalidomide. PF ¶¶ 856–69. Indeed, although Dr. Knowles was initially enthusiastic about apremilast and urged management to pursue the in-licensing

opportunity, he was eventually convinced that GSK should pass on the opportunity because of the connection between apremilast and thalidomide. PF ¶¶ 856–69. Eleven different major pharmaceutical companies responded similarly when Celgene approached them about licensing apremilast and its SelCID technology. PF ¶¶ 848–55. None seized the opportunity. PF ¶¶ 848–55.

A nexus exists between the skepticism of FDA and other pharmaceutical companies and the asserted claims of the '638 and '536 Patents. PF ¶¶ 870–72. The skepticism concerned the potential safety of the apremilast compound, and its suitability for use in treating psoriasis, and was therefore directed at "the workability of the claimed solution" of the asserted patents. *WBIP*, 829 F.3d at 1335. Relying on *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327 (Fed. Cir. 2008), Defendants attempt to dismiss this evidence of nexus by contending that any skepticism of apremilast because of its relationship to thalidomide would have been true of Example 12, which was in the prior art, as well. But in *Muniauction*, the evidence of skepticism was dismissed as lacking the requisite nexus because it came from "market forces"—in that case, investment banks—that benefited from the older technology and thus had reason to downplay any new invention. Here, there is no similar reason to discount the skepticism of FDA, which is charged with guarding the safety and efficacy of marketed drugs. The other entities that were skeptical of apremilast—GSK and the other companies that rejected the apremilast in-licensing opportunity—stood to benefit from apremilast, the *new* technology, but were still skeptical. This skepticism speaks volumes about the non-obviousness of apremilast.

d. Apremilast's unexpected results support non-obviousness.

Unexpected results relative to the prior art may demonstrate non-obviousness. *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1355 (Fed. Cir. 2017).

In comparison to cilomilast, the most advanced PDE4 inhibitor being studied in 1999 and in 2002, apremilast demonstrated unexpected results across several key metrics, which allowed it

to be developed as an effective treatment with limited side effects. PF ¶¶ 873–912. Defendants' argument that unexpected results can be compared only to data from the racemate, and not cilomilast, are baseless. It is improper to require a party to identify and focus on a single prior art reference when arguing a patented invention has demonstrated unexpected properties. *Tris Pharma, Inc. v. Actavis Labs. FL, Inc.*, 755 F. App'x 983, 992 (Fed. Cir. 2019). As a factual matter it is beyond dispute that in 1999 and in 2002, cilomilast was considered the gold standard against which other PDE4 inhibitors were compared; comparisons to cilomilast are thus probative as to what would have been surprising, and therefore not-obvious. PF ¶¶ 873–75.

Apremilast's therapeutic index for emesis, which measures a drug's efficacy relative to an adverse effect, was thirty-one times that of cilomilast, a "thrilling" result for Celgene scientists which set apremilast apart from all other PDE4 inhibitors and indicated that apremilast could succeed where so many other PDE4-inhibiting compounds failed. PF ¶¶ 876–97. Apremilast also demonstrated a PDE4A4 ratio ten times lower than that of cilomilast. PF ¶¶ 898–908. This result indicated apremilast could have dramatically better tolerability than a benchmark drug. PF ¶¶ 902–03. Apremilast's ability to provide efficacious dosing with dramatically less risk of emesis was an unexpected and highly meaningful result given the history of PDE4 inhibitors that were discontinued due to emetic side effects. Defendants' attempts to wave away this clear evidence of non-obviousness by pointing out that the index does not provide data about the entire side effect profile of a drug are meritless—such a metric does not exist. PF ¶ 878.

Apremilast also demonstrated unexpected results relative to the Example 12 racemate: apremilast's PDE4A4 ratio was ten times lower than the racemate—indicating better tolerability—and in testing on mice to assess its efficacy, apremilast demonstrated twenty times greater potency than the racemate, a difference which surprised Celgene scientists, and was far greater than any

difference that could have been anticipated (at most, a two-fold difference) between apremilast and the racemate. PF ¶¶ 909–29.

Defendants' argument that these are merely differences in degree, and not in kind, should be rejected. Courts have found that such numerical increases in potency and decreases in toxicity are evidence that a compound was not obvious.[14] Apremilast demonstrated unexpected properties that made it a vastly better candidate for use as an anti-inflammatory treatment than any PDE4 inhibitor known in the prior art, and apremilast's improved potency, tolerability, and therapeutic index, are precisely the reason it has been successfully developed as a therapeutic drug where the vast majority of other compounds failed. PF ¶¶ 930–32.

A nexus exists between the asserted claims and apremilast's unexpected potency as a PDE4 inhibitor, and apremilast's unexpected ability to be administered in an effective dose while avoiding unacceptable side effects. The potency and side effect profile of apremilast are directly linked to the asserted claims of the '638 Patent, and those properties make use of apremilast to treat psoriasis (as claimed in Claim 6 of the '536 Patent) possible. PF ¶¶ 930–32.

e. The clinical and commercial success of apremilast support non-obviousness.

Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to the POSA. *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). "The

[14] *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017) (discussing "superior stability, solubility, and dissolution" as unexpected results); *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1269 (Fed. Cir. 2007) (unexpected that enantiomer was two-fold more potent than racemic mixture); *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 969–70 (Fed. Cir. 2006) (23% ratio of blackhead removal was unexpected result where prior art resulted in a 4% ratio); *Daiichi Sankyo Co., Ltd. v. Mylan Pharms. Inc.*, 670 F. Supp. 2d 359, 382 (D.N.J. 2009) (claimed compound's 2–4 fold greater potency than prior art compounds was unexpected result).

Court may also look to evidence of [a drug's] clinical success." *Immunex*, 395 F. Supp. at 404.

Otezla has transformed the treatment of moderate-to-severe plaque psoriasis, and has allowed many patients to obtain relief from the symptoms of their disease and regain control of their social and professional lives. PF ¶¶ 933–43. Defendants cherry-picked various aspects of alternative treatments in an attempt to minimize Otezla's clinical benefits, such as lower efficacy in relation to biologics, Otezla's more frequent dosing, and the GI side effects some patients experience early in treatment with Otezla. Defendants failed to show that any of these supposed drawbacks significantly curtailed use of Otezla, nor did they dispute that Otezla plays a valuable role in the armamentarium of psoriasis treatments. PF ¶¶ 940–43.

In fact, Otezla's clinical success has translated to significant commercial success, resulting in roughly 1.7 million prescriptions as of April 2020. PF ¶ 952. Even more telling than the raw prescription numbers is the fact that Otezla's success has taken place in the highly competitive market for psoriasis patients whose disease is not well controlled by topicals and who are candidates for systemic therapy. PF ¶¶ 947–51. Otezla quickly gained a significant share of that market, surpassed generic methotrexate despite that drug's significant cost and formulary advantages, and has become the most prescribed systemic drug for treatment-naïve psoriasis patients, indicating that Otezla is the first choice among health-care providers when a patient's established treatment with another systemic drug is not a factor. PF ¶¶ 947–51. And Otezla has maintained and even expanded its market share despite the launch of five new biologic treatments for psoriasis (including Cosentyx, Taltz, and Skyrizi) by major pharmaceutical companies. PF ¶ 948. Defendants' own economic expert, Mr. Hofmann, does not, and cannot, dispute that Otezla has achieved marketplace success. PF ¶ 947.

Having conceded that Otezla achieved marketplace success, Defendants were left to argue

that there is no nexus between Otezla's success and the asserted claims, because the success was driven by features unrelated to the patented inventions. That argument was not supported by the evidence. As an initial matter, a nexus is presumed between Otezla's clinical and commercial success and the asserted claims of the '638 and '536 Patents because Otezla embodies the claims. *WBIP*, 829 F.3d at 1329; *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1311 (Fed. Cir. 2011); PF ¶¶ 66–67. Moreover, the experts agreed that the merits of Otezla were the biggest driver of prescription decisions. Key therapeutic attributes of Otezla drove demand and are attributable to the use of stereomerically pure apremilast in a pharmaceutical composition to treat psoriasis, as claimed in the '638 and '536 Patents respectively.[15] PF ¶¶ 946, 953, 977–78. Testimony from Drs. Alexis, Vellturo, and Gilmore, and Mr. Hoffman also indicate that precisely these features drove demand for Otezla. PF ¶¶ 798–800, 942, 977–78. The critical role Otezla's attributes played in its clinical and commercial success is further confirmed by physician surveys, in which health-care providers consistently rated Otezla highly in those attributes and indicated the attributes were among their primary reasons for prescribing the drugs. PF ¶¶ 953–58.

Defendants failed to establish that advertising disproportionately contributed to Otezla's success. PF ¶¶ 959–66, 977–78. All of the branded drugs for psoriasis are advertised and Dr. Vellturo's analysis of the relationship between Otezla's share of direct-to-consumer advertising expenditures for psoriasis and psoriatic arthritis treatments, and its share of prescriptions written for those indications, showed that Otezla's advertising relative to its prescription share was similar to, or lower than, that of other treatments, and was lower than a

[15] Defendants argue that objective evidence related to apremilast has no nexus to the '638 and the '536 Patents, because apremilast was known in the prior art. As discussed above, Defendants are incorrect. Stereomerically pure apremilast is a novel feature, and pharmaceutical compositions, and the method of treating psoriasis with it are novel to the '638 and '536 Patents respectively.

number of recently launched therapies. PF ¶¶ 959–63. Defendants did not, and could not, provide any contrary quantitative analysis that shows Otezla disproportionately benefitted from advertising, or other initiatives such as its patient support program or titration starter packs. Instead, Mr. Hoffman identified a handful of Amgen and Celgene documents that he claimed show Otezla disproportionately benefited from advertising or other initiatives, but the documents he cited rarely provide any basis for comparing Otezla to other treatments, and in some instances demonstrate that other psoriasis treatments were marketed more aggressively than Otezla. PF ¶¶ 962. Moreover, any impact advertising had on Otezla's success cannot be divorced from the contributions of the asserted patents, as Dr. Vellturo and Mr. Hoffman both testified that the therapeutic attributes of Otezla traceable to the asserted patents were at the core of Otezla's advertising and detailing messages. PF ¶¶ 964–66.

Defendants' arguments about sampling, patient support programs, and discounting also failed. These initiatives are the norm for branded pharmaceutical products and for psoriasis treatments specifically. PF ¶ 976. Defendants did not show that Otezla benefited more from these initiatives than any other branded psoriasis treatment—on the contrary, physician survey data and the testimony of both dermatology experts indicate that price and insurance coverage issues were obstacles to Otezla's success. PF ¶¶ 967–76.

Finally, Defendants incorrectly alleged that the '358 Patent functioned as a so-called blocking patent to the claimed inventions. The theory of a blocking patent assumes that another party would not be incentivized to develop an invention because they could not commercially exploit the invention without access to a blocking patent. *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1337 (Fed. Cir. 2018); PF ¶ 984. Those are simply not the facts of this case. *First*, the '358 Patent could not have dampened incentives to develop the inventions of the

'638 Patent, because the inventions of the '638 Patent were conceived in October 21, 1999, before the '358 Patent became known. PF ¶ 982. *Second*, even after February 2000, when others became aware of the existence of the '358 Patent, it did not function as a blocking patent to the inventions of the '638 or the '536 Patents because Celgene made a concerted effort to enter into a licensing agreement that would have given the licensee freedom to develop and exploit the inventions of the '358 Patent. PF ¶¶ 984–92. Celgene was willing and eager to license, given its lack of resources and the tremendous costs associated with drug development and launch. PF ¶ 987. Celgene was first to develop the patented inventions and attain commercial and clinical success with Otezla, not because of any blocking effect of the '358 Patent, but because other pharmaceutical companies were not interested in Celgene's technology, and were concerned about apremilast being a thalidomide analog. PF ¶¶ 984–92.

f. Industry acquiescence concerning the '638 Composition and '536 Treatment of Psoriasis Patents supports non-obviousness.

Industry acquiescence may be objective evidence of nonobviousness. *See, e.g.*, *Kowa Co., Ltd. v. Amneal Pharms.*, LLC, No. 14-CV-2758, 2017 WL 10667088, at *8 (S.D.N.Y. Apr. 11, 2017) ("The Court notes that five former defendants . . . involving the '336 patent have settled, indicative of industry acquiescence which 'constitutes a strong showing of [the '336 patent's] validity.'") (citation omitted), *aff'd*, 745 F. App'x 168 (Fed. Cir. 2018). Here, at least sixteen drug manufacturers have expressly admitted that the '638 Patent is valid and enforceable and at least eleven have expressly admitted that the '536 Patent is valid and enforceable. PF ¶¶ 993–1010.

C. Defendants Have Not Proven by Clear and Convincing Evidence That the Asserted Claims of the '536 Psoriasis Patent Would Have Been Obvious.

Claim 6 of the '536 Patent, which claims a method of treating psoriasis with stereomerically pure apremilast, is non-obvious for similar reasons as the asserted claims of the '638 Patent. Defendants' only proposed combination, namely the '358 Patent in combination

with Muller 1998, Dyke 1999, and Marriott 2001, does not render claim 6 obvious.[16] Defendants' obviousness argument was premised on the assumption that the prior art discloses stereomerically pure apremilast with about 97% stereomeric purity. For the same reasons as discussed in Section I.A.2, stereomerically pure apremilast was not disclosed by the '358 Patent and thus was not known by 2002. Defendants have not asserted, and none of Defendants' experts offered an opinion regarding, the obviousness of stereomerically pure apremilast based on the '358 Patent alone. None of the additional references relied on by Defendants disclose or discuss stereomerically pure apremilast, and there is no overlap between the compounds of the '358 Patent and the compounds disclosed in Muller 1998, Dyke 1999, or Marriott 2001. Thus, Defendants did not meet their burden of demonstrating that the POSA would have arrived at stereomerically pure apremilast with a reasonable expectation of success based on any one or combination of the '358 Patent, Muller 1998, Dyke 1999, and Marriott 2001. PF ¶¶ 1124–27. Since stereomerically pure apremilast was novel and non-obvious, the POSA would have been unaware of any of its properties, and thus would not have been motivated to use it in a method of treatment of psoriasis, with a reasonable expectation of success. PF ¶¶ 1124–26.

Even if apremilast were not novel, which it was, Defendants failed to prove that any of the references would have motivated the POSA to use apremilast to treat psoriasis, with a reasonable expectation of success. PF ¶¶ 1081. Given the complete absence of biological data of apremilast

[16] Defendants previously asserted the '358 Patent in combination with either (1) Dyke 1999, Marriott 2001 and Takeuchi; or (2) Dyke 1999, Marriott 2001 and WO '606. None of Defendants' experts opined on these two combinations. PF ¶¶ 1154–55, 1158; *see also* ECF No. 455 at 1 (seemingly confirming that these combinations have been dropped). Regardless, Defendants have not adduced expert opinion concerning these combinations, PF ¶¶ 1154–55, 1158, and did not meet their burden of proving that claim 6 of the '536 Patent would have been obvious in light of either combination. *See Proveris Scientific Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1267 (Fed. Cir. 2008) (expert testimony required to prove invalidity).

(or any compound within the scope of the '358 Patent) and its connection to thalidomide, the POSA would not have reasonably expected that apremilast would have the desirable properties—potency, selectivity, safety, tolerability, or drug-like properties—that would make it suitable to treat a chronic inflammatory disease like psoriasis. PF ¶¶ 1141–43.

None of Defendants' secondary references, Dyke 1999, Marriott 2001 or Muller 1998 remedied the deficiencies of the '358 Patent. Dyke 1999 is a general review article that covers a large number of PDE4 inhibitors under various stages of development at that time, none of which are compounds within the scope of the '358 Patent. PF ¶¶ 1083–94. There was no basis to extrapolate the behavior of one compound based on the behavior of a structurally dissimilar compound, especially where there was no data suggesting that any of the compounds of the '358 Patent have similar biological properties to the compounds of Dyke 1999. PF ¶ 1135. The only example of a PDE4 inhibitor to treat psoriasis is a topical agent developed in 1979, and the POSA would not have reasonably expected that such an agent could be used for oral administration. PF ¶¶ 1088–91.

Marriott 2001, another Celgene reference, discusses certain thalidomide analogs, but none of those that are identified by structure[17] are within the scope of the '358 Patent. PF ¶ 1099. Marriott 2001 discusses studies examining the potential use of thalidomide and its analogs for serious and life-threatening diseases where very few options were available. PF ¶ 1105. In contrast, as of the priority date, therapeutic options were available for psoriasis although they had their shortcomings. PF ¶ 1151. Marriott 2001 also notes that "***safety concerns*** associated with thalidomide will have to be closely monitored during use of the analogs." PF ¶ 1116. Such concern is further exacerbated by the fact that thalidomide is associated with the risk of peripheral

[17] While Marriott 2001 does mention CDC-998, its structure was not disclosed. PF ¶¶ 1109–11.

neuropathy, a serious complication that can be permanent and results from chronic use of the drug. PF ¶ 531. In part because of the peripheral neuropathy warning, the POSA would be concerned about the chronic use of thalidomide analogs for the treatment of psoriasis. PF ¶ 580.

Muller 1998 is another Celgene reference disclosing certain SelCIDs with TNF and PDE4 inhibitory activities, none of which are within the scope of the '358 Patent. PF ¶ 1119. Even within the same structural class of compounds, the activity of one SelCID cannot reliably be used to predict the activity of another. PF ¶¶ 1134–37.

For the above reasons, as of March 2002, Defendants have not proven that the use of stereomerically pure apremilast in a tablet or capsule to treat psoriasis would have been obvious to the POSA over the '358 Patent, combined with Muller 1998, Dyke 1999, and Marriott 2001.

D. Defendants Have Failed to Prove That the Asserted Claims of the '638 Composition Patent Are Invalid for Obviousness-type Double Patenting.

ODP is a "judicially created doctrine" aimed at preventing an "*improper* timewise extension" of a patent right, *In re Braat*, 937 F.2d 589, 592 (Fed. Cir. 1991), and ODP thus bars a patentee from blocking the use of an invention "beyond the statutorily allowed patent term." *Novartis Pharm. Corp. v. Breckenridge Pharm., Inc.*, 909 F.3d 1355, 1362 (Fed. Cir. 2018).

Here, Defendants do not contend that Celgene improperly obtained the '638 Patent to extend the term of any earlier patent covering apremilast. Indeed, Defendants offered no evidence to suggest improper conduct of any kind. PF ¶¶ 1036–57. Instead, they contend that the '638 Patent's statutory patent-term adjustment ("PTA"), awarded pursuant to 35 U.S.C. § 154(b), renders the patent invalid for ODP in light of the earlier-expiring '283 Patent, which claims a crystalline Form A of apremilast. But the *only* reason the '638 Patent expires later than the '283 Patent is because it received two statutorily authorized, and properly calculated, term extensions: a patent-term adjustment (or "PTA") of 609 days, pursuant to 35 U.S.C. § 154(b), and a patent-

term extension (or "PTE") of 1,186 days, pursuant to 35 U.S.C. § 156. PF ¶¶ 1012–35. Defendants' ODP challenge fails on the law and is improper as a matter of equity. And even if the defense were otherwise viable, Defendants did not meet their burden on patentable distinctness.

1. Defendants' Attempt to Use a Judicially Created Doctrine to Cut Short a Statutorily Authorized Time Extension Fails as a Matter of Law.

Defendants ask this Court to use a judge-made doctrine to cut short a statutory term extension, substituting Defendants' policy views for those of the Congress that enacted the Patent Term Guarantee Act of 1999. That Act addressed a problem that arose when Congress changed the rules for calculating a patent's term. While examination delays did not affect a patent's term under the earlier, 17-years-from-*issuance* regime, the switch to a term of 20 years from *filing* a patent application meant that such delays by the Patent Office "consumed the effective term of a patent." *Wyeth v. Kappos*, 591 F.3d 1364, 1366 (Fed. Cir. 2010). Congress thus enacted a remedy in § 154(b)(1): mandatory patent-term adjustment whenever the Patent Office fails to meet statutory deadlines, such as the 14-month deadline for issuing a first office action or the three-year deadline for concluding prosecution. *See Wyeth*, 591 F.3d at 1367. The statute reflects Congress's intent to "guarantee[] diligent applicants at least a 17-year term" by extending term to compensate for examination delays. H.R. Rep. No. 106-287, pt. 1, at 50 (1999).

Judge-made ODP doctrine cannot undo this legislative choice. Indeed, Defendants' ODP challenge is foreclosed by the reasoning of *Novartis AG v. Ezra Ventures LLC*, 909 F.3d 1367 (Fed. Cir. 2018). *Ezra* considered whether a patent was invalid for ODP because its statutory PTE caused it to expire after another patent covering essentially the same invention. *See* 909 F.3d at 1373. The *Ezra* Court held that ODP "does not invalidate a validly obtained" PTE, *id.*, and it specifically rejected defendants' attempt to use a "judge-made doctrine" to "cut off a statutorily-authorized time extension," *id.* at 1375.

The result here should be the same. Like PTE, PTA is a statutorily authorized time extension that "restore[s] the value of the patent term that a patent owner loses" due to review by an administrative agency. *Ezra*, 909 F.3d at 1369. Both § 154(b) and § 156 use the same mandatory language, providing that patent term "shall be extended" when the requirements are met. And both reflect carefully tailored legislative decisions to adjust the statutory term of a patent due to agency delays beyond the patent owner's control. *Cf. O'Melveny & Myers v. FDIC*, 512 U.S. 79, 85 (1994) (courts should not "adopt a court-made rule to supplement federal statutory regulation that is comprehensive and detailed"). In particular, PTE restores term lost to delays arising from agency (*e.g.*, FDA) review of a patented product, and PTA restores term lost to pre-issuance delays arising from agency (*i.e.*, Patent Office) review of a patent application. PF ¶¶ 1017–23. Either way, a patent receives additional term based on agency delays, pursuant to statutory formulas implemented by the Patent Office. PF ¶¶ 1022–23. Consistent with *Ezra*'s holding with respect to § 156, ODP also cannot cut short the extension granted by statute under § 154(b). Accordingly, the '283 Patent is not a proper ODP reference for the '638 Patent.

Chief Judge Wolfson recently rejected a similar effort by Zydus to invoke ODP to cut short a PTA in *Mitsubishi Tanabe Pharma Corp. v. Sandoz, Inc.*, Civ. No. 17-5319, 2021 WL 1845499 (D.N.J. Apr. 7, 2021), holding that the asserted ODP reference patent was "not a proper reference" under Federal Circuit law. *Id.* at *29.[18] Ultimately, Chief Judge Wolfson was "swayed by the Federal Circuit's observation that 'a judge made doctrine' should not be used to 'cut off a statutorily-authorized time extension.'" *Id.* (quoting *Ezra*, 909 F.3d at 1375). So, too, here.

Mitsubishi found no relevant distinction for ODP purposes between a statutory term

[18] *Mitsubishi* also observed that the language in *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr.*, 764 F.3d 1366 (Fed. Cir. 2014), on which Zydus relied (as Defendants do here) was "dicta" that had subsequently been distinguished. 2021 WL 1845499, at *29 n.43.

extension for FDA delay under § 156 (as in *Ezra*) and one for Patent Office delay under § 154(b). 2021 WL 1845499, at *29 & n.45. As Defendants do here, Zydus had sought to distinguish *Ezra*, arguing that PTA cannot be awarded "beyond the expiration date specified in [a terminal] disclaimer," 35 U.S.C. § 154(b)(2)(B), whereas extensions under § 156 are not limited by terminal disclaimers. *Mitsubishi*, 2021 WL 1845499, at *29 n.45. But Chief Judge Wolfson recognized that terminal disclaimers simply limit the extent of a PTA where such disclaimers "had previously been filed," but no disclaimer had been filed in connection with the patents at issue in *Mitsubishi*. *Id.*

Terminal disclaimers are equally irrelevant here. Where an applicant takes advantage of a terminal disclaimer to overcome a rejection for ODP raised by a patent examiner, the rules for calculating patent-term adjustment bar the applicant from recovering via PTA the portion of the patent term that was disclaimed by the patent owner's filing of a terminal disclaimer. *See* 35 U.S.C. § 154(b)(2)(B). Here, Celgene did not file a terminal disclaimer in connection with the '638 Patent, so the date to which PTA may extend is not so limited. PF ¶ 1029.

Because the difference in patent term of the '638 Patent and the '283 Patent is solely due to statutorily mandated PTA and PTE, Defendants' ODP challenge fails as a matter of law.

2. Defendants' ODP challenge Also Fails as a Matter of Equity.

As an "equitable doctrine," *see Immunex*, 964 F.3d at 1059, the application of ODP is often driven by the facts and circumstances of a particular case. *Cf., e.g., Gasser Chair Co. v. Infanti Chair Mfg. Corp.*, 60 F.3d 770, 773 (Fed. Cir. 1995) (courts in equity "look to all the facts and circumstances of the case and weigh the equities"). In assessing whether to apply ODP, courts have often looked to the reasons why a challenged patent expires after an asserted double-patenting reference. For example, the Federal Circuit has declined to apply ODP where the patents expired at different times due to a change in "patent term law," rather than "patent prosecution gamesmanship." *Breckenridge*, 909 F.3d at 1362, 1364; *see also Ezra*, 909 F.3d at 1374 (finding

"no potential gamesmanship issue" for statutory term extension). And Judge Cecchi recently explained that, when a patent's challenged term results from "an act of Congress, rather than improper gamesmanship by the patentee," the "statutory term . . . may not be cut short." *See Immunex*, 395 F. Supp. 3d at 422 (internal quotation marks omitted). In other words, differences in expiration dates resulting from legislative choices do not give rise to ODP.

Here, it undisputed that the difference in expiration dates between the '638 and '283 Patents is not the result of any prosecution gamesmanship or improper conduct by Celgene, as Mr. Smith (an expert in Patent Office policy, practice, and procedure) testified. PF ¶¶ 1036–57. The '638 Patent expires later than the '283 Patent solely because it was properly awarded two statutory time extensions, for delays outside Celgene's control. PF ¶¶ 1012–35.

Defendants' challenge here stands out as particularly unsupportable on the equities, for two additional reasons. *First*, as Mr. Smith explained in his unrebutted testimony, but for Patent Office delays, much of the '638 Patent's challenged PTA would instead be unchallenged PTE. PF ¶¶ 1050–52. And if there were *only* PTE, there would be no ODP challenge at all, given the Federal Circuit's ruling in *Ezra*. But Celgene had no control over the delays that gave rise to the specific mix of PTA and PTE it received, which further supports the equities of denying Defendants' ODP challenge. PF ¶ 1053.

Second, here, Defendants seek to cut short the term of protection for Celgene's fundamental invention of stereomerically pure apremilast, claimed in the '638 Patent, based on a separately patentable improvement pursued years later in '283 Patent, simply because of a patent-term adjustment traceable to the Patent Office's delays in examination. PF ¶¶ 1054–56. This challenge runs contrary to the basic equitable principles of ODP. As the Federal Circuit has explained, an "applicant (or applicants), who files applications for basic and improvement patents should not be

penalized by the rate of progress of the applications through the PTO, a matter over which the applicant does not have complete control." *Braat*, 937 F.2d at 593; PF ¶ 1057.

3. Defendants Have Not Met Their Burden on Patentable Distinctness.

Finally, even setting aside the threshold legal and equitable principles above, Defendants have failed to carry their burden to show by clear and convincing evidence that the inventions claimed in Claims 3 and 6 of the '638 Patent are patentably indistinct from the invention claimed in Claim 1 of the '283 Patent. A basic principle of the distinctness analysis is that "each claim is an *entity* which must be considered *as a whole*." *Gen. Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1274 (Fed. Cir. 1992). Defendants have failed to offer evidence that comports with this basic principle. Defendants' only evidence is the testimony of Dr. Gribble, PF ¶ 1059, but Dr. Gribble simply picked out individual elements of the claims and compared them, rather than analyzing the claimed subject matter as a whole—precisely what *General Foods* forbids. PF ¶¶ 1059–60. Indeed, he did not even *mention* "distinctness." PF ¶ 1061. Defendants simply failed to provide the analysis necessary to carry their burden. PF ¶¶ 1058, 1062.

E. Defendants Have Not Proven by Clear and Convincing Evidence That the Asserted Claim of the '536 Psoriasis Patent Is Invalid for Lack of Enablement or Written Description.

Defendants have not shown that claim 6 of the '536 Patent is invalid for failing to satisfy the written description and enablement requirements of 35 U.S.C. § 112(a). Amgen made a motion on this issue under Fed. R. Civ. P. 52(c) on June 23, 2021. Trial Tr. at 1293:1–1294:16. On July 1, 2021, Amgen submitted a memorandum in support of its motion, the contents of which are incorporated by reference. *See* Pl's Memo. (ECF No. 462).

Defendants also cannot stitch together an invalidity defense from snippets of cherry-picked testimony from Dr. Gilmore's examination, as Defendants alluded to in oral opposition to the motion on this issue. *See* Trial Tr. at 1294:19–1296:2. None of Dr. Gilmore's testimony was

germane to written description or enablement, PF ¶¶ 1166–68, and even if it was germane, Defendants cannot meet their burden of clear and convincing evidence through general and conclusory testimony. *See WBIP*, 829 F.3d at 1338–39.[19] Further, Defendants cannot remedy the deficiencies in their expert testimony by presenting "attorney argument to suggest that a [POSA] would not have understood the claimed invention to be adequately described" or enabled. *See AAT Bioquest, Inc. v. Texas Fluorescence Labs., Inc.*, 2015 WL 1738402 , at *5 (granting summary judgment of non-invalidity based on asserted lack of written description); *see also Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1068 (Fed. Cir. 2005) ("Unsubstantiated attorney argument regarding the meaning of technical evidence is no substitute for competent, substantiated expert testimony."). Defendants have simply failed to meet their burden of proof.

If the Court is inclined to allow Defendants to advance their defense through attorney argument, the asserted claim of the '536 Patent is enabled. Each element of the claim is stated expressly in the specification, thus providing written description support. JTX-7 at 3:37–50 (the invention "encompasses the use of [apremilast] to treat diseases or disorder ameliorated by the inhibition of PDE4," including psoriasis), 15:20–26 (the invention may be "suitable for oral administration," including in tablet or capsule form), 16:13–19 (saying that the dose amount of apremilast should be "specifically, between about 10 mg and 200 mg per day," and should either be in a single dose or divided dose), 5:64–6:9 (the stereomerically pure compound will be "most preferably greater than about 97% by weight of one stereoisomer"). Moreover, the specification provides ample data—something missing from the '358 Patent—to support that the POSA would

[19] The Federal Circuit recently emphasized that "[c]onclusory expert testimony is [] inadequate as substantial evidence in other areas of patent law" where a party bears the burden of proof. *See TQ Delta, LLC v. CISCO Sys., Inc.*, 942 F.3d 1352, 1359 n.5 (Fed. Cir. 2019) (addressing obviousness and collecting cases for enablement, written description, anticipation, and infringement).

be able to practice the claimed method without undue experimentation. PF ¶ 1188.

1. Defendants' Enablement Challenge to the '536 Patent Is Inconsistent With Defendants' Reliance on the '536 Patent In Their Obviousness Challenge to the '541 Patent and Should Be Rejected.

As Defendants are aware, "prior art references are presumed to be enabled," *see* Defs.' Pre-Trial Br. (ECF No. 398) at 17 *(*citing *Proctor & Gamble Co. v. Nabisco Brands, Inc.*, 711 F. Supp. 759, 772 (D. Del. 1989)). Yet Defendants are trying to have it both ways: arguing that the '536 Patent claims lack written description and enablement, while simultaneously relying on the '536 Patent to assert obviousness of another Otezla patent. In their challenge to the '541 Patent, Defendants argued that "[b]ased on the disclosures of the '536 Patent, a POSA would have been motivated with a reasonable expectation of success to use and administer to patients stereomerically pure apremilast, including stereomerically pure apremilast comprising greater than about 98% by weight of (+) isomer." *See* Defs.' Pre-Trial Br. (ECF No. 398) at 77. Indeed, Defendants' inconsistent arguments demonstrate the unsubstantiated nature of their enablement challenge. For this additional reason, this defense should be dismissed.

2. The Predicate for Defendants' Conditional Argument Regarding Written Description and Enablement Is Not Met.

Finally, Defendants' argument on written description and enablement is expressly conditioned upon Amgen asserting that the prior art does not render claim 6 of the '536 Patent obvious because the prior art fails to disclose human clinical trial data teaching a therapeutically effective amount of apremilast to treat diseases and disorders ameliorated by PDE4 inhibition, including psoriasis.[20] Defendants' condition precedent was never met. PF ¶¶ 1164–65. When

[20] Defendants presented their written description and enablement arguments in their pre-trial brief subject to this condition. *See* Defs.' Pre-Trial Br. (ECF No. 398) at 49 ("**To the extent** the asserted claim of the '536 patent is found not obvious **because the prior art fails to disclose clinical data** teaching the efficacy of apremilast in treating psoriasis, the specification of the '536 patent itself

Amgen's expert Dr. Knowles was directly asked whether he "conclude[d] that any prior art reference failed to render claim 6 of the '536 Patent obvious simply because it failed to disclose human clinical data teaching a therapeutically effective amount of apremilast to treat diseases and disorders ameliorated by the inhibition PDE4 including psoriasis," Dr. Knowles answered "No." Trial Tr. at 1700:19–24 (Knowles Direct 6.25.21).

Further, not only has Amgen never asserted that clinical studies are necessary to show the success of a method of treating psoriasis using stereomerically pure apremilast, but the Federal Circuit has repeatedly held that this position is incorrect. *See, e.g.*, *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329, 1343 (Fed. Cir. 2010) (affirming validity of method of treatment patents for which a confirming clinical trial "was ongoing at the time the application was filed"); *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995) ("Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans."). For this additional reason, the predicate basis for Defendants' conditional argument has no basis, and Defendants' conditional argument must fail.

II. The Asserted Claims of the '101 Form B Patent and '283 Form A Patent Are Infringed and Not Invalid.

Amgen asserts two patents relating to specific crystalline forms of apremilast: the '101 Patent, which relates to Form B, and the '283 Patent, which relates to Form A. Claims 1 and 15 of the '101 Patent are asserted against Sandoz and Zydus, and claims 2 and 27 of the '283 Patent are

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fails to satisfy the written description requirement"), 50 ("**To the extent clinical data are required** to show the effectiveness of a PDE4 inhibitor in treating psoriasis, a POSA would have to conduct undue experimentation to arrive at the claimed method") (emphasis added). In addition, as explained in detail in Amgen's Motion for Judgment on Partial Findings on this issue, (ECF No. 462) at 7–8, Defendants consistently held this same position in previous email correspondence with Amgen and in Defendants' expert reports.

asserted only against Zydus. Zydus disputes infringement of the '101 Patent, Sandoz does not. As explained below, test results demonstrated that Zydus's proposed ANDA product contains Form B of apremilast and infringes the asserted claims of the '101 Patent, and Defendants have not met their burden of proving that the asserted claims of either patent are invalid.

A. Defendants Infringe the Asserted Claims of the '101 Form B Patent and '283 Form A Patent.

Sandoz has stipulated to infringement of claims 1 and 15 of the '101 Patent. PF ¶¶ 1234–35. Zydus has stipulated to infringement of claims 2 and 27 of the '283 Patent, PF ¶¶ 1470–71, but contests infringement of claims 1 and 15 of the '101 Patent.

1. Zydus Infringes Claims 1 and 15 of the '101 Form B Patent.

Claim 1 of the '101 Patent claims enantiomerically pure Form B of apremilast, having XRPD peaks at 10.1, 13.5, 20.7, and 26.9 degrees 2-theta. PF ¶ 33. Claim 15 of the '101 Patent claims a solid pharmaceutical composition comprising the Form B recited in claim 1. PF ¶ 34. Because Zydus admits its ANDA Products are solid pharmaceutical compositions containing enantiomerically pure apremilast, PF ¶¶ 1256–57, and that an XRPD analysis of Form B inherently generates peaks at 10.1, 13.5, 20.7, and 26.9 degrees 2-theta, PF ¶ 1252, the question for infringement is whether Zydus's ANDA Products contain Form B of apremilast.

Testing of samples of Zydus's API shows the presence of Form B.[21] PF ¶¶ 1258–1304. The chain of custody of these samples, and Zydus's own internal testing, shows that these samples are representative of the API that will be in the ANDA Products that Zydus intends to sell. PF 1305–31. Zydus's ANDA Products will contain Form B because Zydus's API contains Form B, and Zydus's ANDA Products will be manufactured using Zydus's API. PF ¶¶ 1332–36. Testing of

[21] Claims 1 and 15 of the '101 Patent do not require a minimum amount of Form B. PF ¶ 1262.

samples of Zydus's ANDA Products are consistent with the presence of Form B.[22] PF ¶¶ 1337–56. Amgen has proven by a preponderance of evidence that Zydus ANDA Products infringe claims 1 and 15 of the '101 Patent. PF ¶¶ 1364–66.

a. Legal standard for infringement.

Anyone who "makes, uses, offers to sell, or sells any patented invention . . . , within the United States or imports into the United States a patented invention during the term of the patent," without permission by the patent owner, is an infringer. 35 U.S.C. § 271(a). To find infringement, each and every element of the asserted claim must be present in the accused product. *Carroll Touch Inc. v. Electro Mech. Sys., Inc.*, 15 F.3d 1573, 1576 (Fed. Cir. 1993) (citation omitted). Because an ANDA applicant has not yet marketed its drug product, the court's infringement analysis involves a "hypothetical inquiry," *Glaxo Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997), that focuses "on the product that is likely to be sold following FDA approval," *Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). The patentee must prove infringement by a preponderance of the evidence. *See Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008).

XRPD analysis of Zydus's API is probative of whether Zydus's ANDA Products will contain From B because, according to Zydus's own documents, "the polymorphic form of the drug substance (apremilast) in the drug product (apremilast tablets) remains unchanged after manufacturing of the drug product and upon storage." PF ¶ 1334. *See Kowa Co., Ltd. v. Amneal Pharms., LLC*, No. 14-CV-2758, 2017 WL 10667089, at *40–47 (S.D.N.Y. Sept. 19, 2017) (finding analyzed API batches were "representative of the polymorphic form of the API in

[22] Zydus's own internal specifications for its API and ANDA Products permit the presence of Form B. PF ¶¶ 1357–60, 1362. Thus, if a sample of Zydus's API or ANDA Products contains Form A and Form B, it would pass Zydus's specification. PF ¶¶ 1361, 1363.

[Defendant's] proposed ANDA product" because API manufacturer "represented to FDA that its [API] remained stable [during] the drug manufacturing process" and therefore concluding that the ANDA product infringed claims to a crystalline form based on XRPD analysis of the API).

b. Testing shows that Form B is present in Zydus's API.

XRPD testing shows that Form B is present in Zydus's API (and thus its ANDA Products). PF ¶¶ 1258–60, 1233–36. Zydus produced samples of its apremilast API exhibit batches[23] to Amgen's counsel. PF ¶ 1264. Amgen's expert Dr. Gozzo tested Zydus's API samples using synchrotron-XRPD. PF ¶¶ 1266–67. Amgen's expert, Prof. Myerson, analyzed Dr. Gozzo's data and determined that it demonstrates that every sample of Zydus's API contained Form B with the claimed peaks. PF ¶¶ 1227, 1261, 1282–89. The presence of Form B in Zydus's API samples is further confirmed by the presence of all twelve XRPD peaks that the '101 Patent identifies as characteristic of Form B. PF ¶¶ 1301–02.

Zydus does not dispute that the peaks Prof. Myerson relies on appear in Dr. Gozzo's diffractograms for Zydus's API samples, and Zydus's own expert, Dr. Miller, admitted he cannot rule out the presence of Form B. PF ¶ 1303. Instead, Zydus argues these peaks do not prove Form B is present because they could have been generated by a combination of Forms A and F. This argument fails because all nine samples of Zydus's API samples include a peak at 12.4 (as Dr. Miller admits), and six of nine samples also have peaks at 6.0, 10.7, and 13.0—which can only be generated by Form B and cannot be generated by Forms A or F. PF ¶¶ 1230, 1250–51, 1290–98.

c. Samples of Zydus's API were representative of the API in Zydus's ANDA Product when Dr. Gozzo tested them.

When an ANDA product sample is tested for infringement, "the critical inquiry is whether

[23] Exhibit batches are representative batches of the API and ANDA Product made by an ANDA filer and used to generate data submitted to FDA as part of the ANDA. *See* PF¶¶ 1280, 1347.

it is representative of what is likely to be approved and marketed." *Merck Sharp & Dohme Corp. v. Amneal Pharms., LLC*, 881 F.3d 1376, 1385 (Fed. Cir. 2018). Here, Dr. Gozzo tested samples from exhibit batches of the API made by Zydus. PF ¶¶ 1273,1280. Zydus does not dispute that those exhibit batches are representative of the API in its ANDA Products. Rather, Zydus contends the *individual samples* were not representative of the API that will be used to manufacture Zydus's ANDA Products *at the time* Dr. Gozzo tested them—because she tested them after they had expired and because they were purportedly mishandled before she tested them. Neither argument has merit.

Prof. Myerson explained that Zydus's exhibit batches, when tested by Dr. Gozzo, could have been used to make batches of Zydus's ANDA Products. PF ¶¶ 1306, 1320. Dr. Gozzo tested the samples of Zydus's API in June 2020, 34 months after they were manufactured in July 2017. PF ¶¶ 1266, 1308. According to Zydus's ANDA, Zydus's API has a retest date, and Zydus's long-term stability studies contemplate using API batches up to 60 months after manufacture so long as they continue to pass their retest specification. PF ¶¶ 1307, 1312. Zydus does not dispute that FDA and ICH guidelines permit an API batch to be used to manufacture ANDA Products as long as the API batch passes its specification upon retesting. PF ¶¶ 1315, 1318. Zydus's own data shows that the same batches of its API that were tested by Dr. Gozzo passed Zydus's specification 36 months after manufacture and two months after Dr. Gozzo's testing. PF ¶¶ 1313, 1316–17. Dr. Miller did not dispute that these batches passed Zydus's specification 36 months after manufacture or that Zydus could have manufactured ANDA Product batches from those API batches at 36 months. PF ¶ 1319. Dr. Gozzo's XRPD data further confirms that the tested samples complied with Zydus's XRPD specification when she analyzed them. PF ¶ 1304.

Prof. Myerson explained that the samples tested by Dr. Gozzo were stored consistently with Zydus's storage requirement (in tightly closed containers at temperature below 25°C) prior

to testing. PF ¶¶ 1309, 1311, 1320–31. Before Dr. Gozzo tested them, the API samples were stored in their original, sealed, undamaged foil pouches. PF ¶¶ 1328–29. Before she received them, they were stored in climate controlled environments, and then shipped to her in temperature-controlled packaging, where she stored and prepared them for testing under controlled conditions. PF ¶¶ 1321, 1326–27, 1330. There is no evidence these samples were ever exposed to temperatures greater than 25 degrees Celsius. PF ¶ 1322.

Moreover, Prof. Myerson explained that a minor temperature excursion beyond 25 degrees Celsius would not have changed the form of apremilast in Zydus's API because a minor temperature change cannot change the polymorphic form present in Zydus's API. PF ¶¶ 1323–24. Zydus offered no evidence to the contrary. Zydus's expert Dr. Miller conceded that he could not identify any conditions under which Form A could or would convert to Form B. PF ¶ 1325. Thus, he had no basis for suggesting such a change may have occurred because of the way the samples were stored. Moreover, he was not qualified as an expert in pharmaceutical handling, pharmaceutical storage, pharmaceutical packaging, or crystallization. PF ¶¶ 151–53, 1325. His opinions that the samples that Dr. Gozzo tested were not representative are therefore mere speculation at best, and should be disregarded as lay opinion. *Apple, Inc. v. Samsung Elecs. Co.*, No. 11-CV-01846-LHK, 2013 WL 5955666, at *2 (N.D. Cal. Nov. 6, 2013) ("Under Federal Rule of Evidence 702, experts may not make expert conclusions about areas outside their expertise.").

d. Results from testing Zydus's ANDA Product are consistent with the presence of Form B.

Zydus's ANDA Products will contain Zydus's API and, thus, also contain Form B apremilast. PF ¶¶ 1333–1336. As Prof. Myerson explained, the diffractograms and peak lists for every sample of Zydus's ANDA Products analyzed by Dr. Gozzo confirm the presence of three of the four XRPD peaks recited in the claims—10.1, 13.5, and 26.9 degrees 2-theta. PF ¶ 1353. Prof.

Myerson explained that the 20.7 peak is also present but is below the limit of detection in Dr. Gozzo's peak lists and diffractograms. PF ¶ 1355. Because the API makes up only 8.67% by weight (the remaining 91.33% is the contribution of inactive ingredients) of Zydus's ANDA Product, it is difficult to detect many of the smaller peaks generated by Form B in the ANDA Products that are seen in the API samples, including the 20.7 peak. PF ¶¶ 1241, 1351, 1354. But they are still there: Prof. Myerson determined that Form B contributed to the peaks at 10.1, 13.5, and 26.9, and generated a peak at 20.7 (albeit below the limit of detection) based on the API data. PF ¶¶ 1229, 1353, 1355. The API data is probative of what is in the ANDA Products because the API batches that Dr. Gozzo tested were the same batches that were used to manufacture the ANDA Products batches that Dr. Gozzo tested. PF ¶¶ 1347–50, 1365.

Although the samples of Zydus's ANDA Products were tested after their 24-month proposed expiration date, Prof. Myerson explained that this did not impact his analysis because the API in Zydus's ANDA Products would still have met Zydus's API specification, as demonstrated by Zydus's 36-month API stability testing. PF ¶ 1352. Zydus offered no contradictory evidence and or reason why the crystalline form of apremilast in samples of its ANDA Product would change 24 months after manufacture. Accordingly, Dr. Gozzo's testing of Zydus's ANDA Products is probative of infringement. *In re Omeprazole Patent Litig.*, 490 F. Supp. 2d 381, 495 (S.D.N.Y. 2007), *aff'd*, 536 F.3d 1361 (Fed. Cir. 2008) ("[T]he Court sees no reason to assume that on the date a product is no longer within the FDA-required shelf life for the purposes of commercialization, it also ceases to be structurally representative of the product.").

B. The Asserted Claims of the '101 Form B Patent and '283 Form A Patent Are Not Invalid.

Defendants argue that claims 1 and 15 of the '101 Patent are obvious and invalid for ODP, and Zydus further argues that claims 2 and 27 of the '283 Patent are anticipated and obvious.

Defendants rely primarily on a publication from the same patent family as the '101 and '283 Patents—the '052 Publication from 2003—which contains Example 2, describing the synthesis of crystalline apremilast. But Example 2 does not just describe the synthesis of *a* crystalline form of apremilast: it *inherently produces* Form B. Because Example 2 also appeared in the earliest application leading to the '101 Patent—the '515 Provisional from 2002—this, in turn, means that the asserted claims of the '101 Patent are entitled to claim priority to the earlier '515 Provisional application. The net result is that the '052 Publication is not prior art to the '101 Patent, and all of Defendants' invalidity theories for that patent fail. Moreover, Zydus's anticipation and obviousness challenges against the '283 Patent also fail because both challenges are premised on Example 2 producing Form A of apremilast, when, in fact, it produces Form B. Indeed, Defendants' validity challenges face an especially uphill climb given that the Patent Office issued the '101 and '283 Patents after considering another application in the same family, the '049 Publication, with the same disclosures as the '052 Publication, including Example 2. PF ¶ 1367.

That Example 2 inherently results in Form B is uncontroverted. The results of thirteen experiments that faithfully replicated Example 2 were submitted to the EPO by three pharmaceutical companies during an opposition to a related European patent. All experts agreed that these thirteen experiments produced Form B. And Amgen's expert, Prof. Myerson, explained that variations in the thirteen experiments accounted for the different ways the POSA might follow Example 2, confirming that Form B is the inherent result of practicing Example 2. As a result, the claims of both the '101 Patent and the '283 Patent are not invalid.

1. Defendants Did Not Prove That Claims 1 and 15 of the '101 Form B Patent Are Invalid As Obvious.

Defendants argued at trial that the asserted claims of the '101 Patent are obvious over two combinations of references, both of which involve the '052 Publication. PF ¶¶ 1367–71. To use

the '052 Publication (published on October 2, 2003, PF ¶¶ 1368, 1425) as an obviousness reference, Defendants argue that the asserted claims of the '101 Patent have a priority date of March 27, 2008 (the filing date of the continuation-in-part application that issued as the '101 Patent). If claims 1 and 15 are instead entitled to a March 20, 2002 priority date (the date of the '515 Provisional), then the '052 Publication is not prior art, PF ¶¶ 1425–1432. *See* 35 U.S.C. § 102(a) (pre-AIA); *see also Mahurkar*, 79 F.3d at 1576. Defendants' obviousness arguments thus reduce to a question of whether claims 1 and 15 of the '101 Patent are entitled to claim priority to March 20, 2002 through the '515 Provisional.[24] Because the evidence showed that the asserted claims *are* entitled to the March 2002 priority date, Defendants' obviousness challenges fail.

a. Claims 1 and 15 of the '101 Form B Patent are entitled to a priority date of March 20, 2002.

Claims from a later filed application are entitled to the priority date of an earlier application properly cited on the face of the patent if the earlier application provides written description and enablement support for the claims in the later application. *See* 35 U.S.C. §§ 112, 120; *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306 (Fed. Cir. 2008). As the party asserting an earlier priority date, Amgen bears the burden of production. *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1328–29 (Fed. Cir. 2008). Amgen accordingly came forward with evidence that the '515 Provisional is correctly cited on the '101 Patent, PF ¶ 1369, and the disclosure of Example 2 in the '515 Provisional provides written description and enablement support for claims 1 and 15, PF ¶¶ 1372–1424, as explained below. This shifted the burden back to Defendants to prove ***by clear and convincing evidence*** that claims 1 and 15 of the '101 Patent are not entitled to the March 20, 2002 priority date. *Tech. Licensing*, 545 F.3d at 1328–29. Defendants have not met their

[24] Defendants did not offer any expert testimony that claims 1 and 15 of the '101 Patent are invalid if those claims are entitled to a priority date of March 20, 2002. PF ¶ 1429.

burden.[25] Thus, claims 1 and 15 of the '101 Patent are entitled to a priority date of March 20, 2002.

(1) Example 2 satisfies the written description requirement for claims 1 and 15 of the '101 Form B Patent.

The '515 Provisional satisfies the written description requirement for claims 1 and 15 of the '101 Patent because the inventors possessed a crystalline form of apremilast that necessarily results from practicing Example 2: Form B with the claimed XRPD peaks. Defendants argued in their pretrial brief that the '515 Provisional does not provide written description because it does not expressly recite Form B with the recited XRPD peaks. Defs. Pretrial Br. at 56 (citing *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353 (Fed. Cir. 2010)). Defendants are wrong: their recitation of the law is incomplete and fails to address the doctrine of inherent disclosure. Under the Federal Circuit's "doctrine of inherent disclosure, when a specification describes an invention that has certain undisclosed yet inherent properties, that specification serves as adequate written description to support a subsequent patent application that explicitly recites the invention's inherent properties." *Yeda Rsch. & Dev. Co. v. Abbott GMBH & Co. KG*, 837 F.3d 1341, 1345 (Fed. Cir. 2016); *see also Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1309 (Fed. Cir. 2015) ("A claim that recites a property that is necessarily inherent in a formulation that is adequately described is not invalid as lacking written description merely because the property itself is not explicitly described."). Indeed, *Yeda* and *Allergan* both cite *Ariad* as providing the general standard for written description before going on to explain how their application of the doctrine of inherent disclosure is consistent with the law of written description set forth in *Ariad*. *Yeda*, 837 F.3d at 1344–45; *Allergan*, 796 F.3d at 1308. The doctrine of inherent disclosure is thus part of the controlling law of written description and must be applied in determining whether the '515

[25] Prof. Steed, Defendants' only expert on the invalidity of the '101 Patent, testified that he was not offering an opinion on lack of enablement of claims 1 and 15 of the '101 Patent. PF ¶ 1423.

Provisional provides written description support for the asserted claims of the '101 Patent.

(a) The POSA would have understood the inventors were in possession of the solid apremilast resulting from Example 2 of the '515 Provisional.

Example 2 of the '515 Provisional discloses a chemical synthesis of apremilast. PF ¶ 1372. In the final step, solid apremilast is "recrystallized from a binary solvent containing ethanol (150 mL) and acetone (75 mL)," (JTX-43 at JTX-43_29) which is dried to yield apremilast that is enantiomerically pure (98% ee). PF ¶¶ 1373–74. The POSA would have understood as of March 20, 2002, that the inventors were in possession of the solid, enantiomerically pure apremilast of Example 2, including its inherent properties. PF ¶ 1413. The POSA would have further understood that the solid, enantiomerically pure apremilast of Example 2 was crystalline. PF ¶¶ 1414–19. All experts agree that the inventors were in possession of the solid apremilast of Example 2 and Prof. Myerson and Dr. Sacchetti agree that the solid apremilast of Example 2 is crystalline. PF ¶¶ 1413–14. It is undisputed that conducting an XRPD analysis of crystalline forms was routine as of March 20, 2002 and results in a unique diffraction pattern inherent to the crystalline form being analyzed and can be used to distinguish the given crystalline form from other forms. PF ¶¶ 1415–17.

(b) Example 2 of the '515 Provisional inherently results in Form B of apremilast.

Testing performed by multiple pharmaceutical companies, including one of the two remaining defendants in this case, confirms that Example 2 inherently results in Form B. PF ¶¶ 1380–1412. In a proceeding before the EPO, three generic pharmaceutical companies (Teva, Zentiva, and Lek, a Sandoz subsidiary, PF ¶ 1393) submitted experimental protocols and resulting data for thirteen replications of Example 2 of the '515 Provisional.[26] PF ¶ 1383. As Prof. Myerson

[26] The data submitted by the generics state that the experiments replicate Example 2 of the '049 Publication, but it is undisputed that Example 2 is word for word the same in the '515 Provisional,

explained, using typical industry recrystallization practices, the thirteen replications varied certain recrystallization parameters that were not specified in Example 2, including stirring time after cooling, stirring temperature, cooling time, and ethanol grade. PF ¶¶ 1383–97. All thirteen replications resulted in Form B having an XRPD diffraction pattern with the peaks recited in '101 Patent claim 1. PF ¶¶ 1383–97, 1419. Prof. Myerson testified that this shows that, even accounting for ways a POSA would have routinely varied undefined parameters of Example 2, Example 2 would have inherently resulted in Form B apremilast. PF ¶¶ 1397, 1412. Thus, the procedure of Example 2 of the '515 Provisional, as understood by the POSA, inherently produces Form B and therefore provides written description support for claims 1 and 15 of the '101 Patent. PF ¶¶ 1413–21.

Defendants' expert, Prof. Steed, does not dispute that all thirteen experiments faithfully replicated Example 2, that Form B resulted from all thirteen experiments, or that the EPO found that Example 2 inherently results in Form B. PF ¶¶ 1384–85, 1388–89, 1392–94. Prof. Steed's only additional commentary on these experiments was to observe that Celgene also submitted experiments and that Celgene represented to the EPO that its experiments purportedly replicated Example 2 and resulted in Form C. Prof. Steed, however, did not form an independent opinion on whether Celgene's experiments actually replicated Example 2 or whether Celgene actually obtained Form C. PF ¶¶ 1408–09.

Prof. Myerson evaluated the description of the Celgene experiments as well as its representations to the EPO, and explained that Celgene did not actually replicate Example 2 because Celgene's experiments used a starting material with a different purity from that specified

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the '049 Publication, the '052 Publication, the '638 Patent, the '940 Patent, the '101 Patent, and the '283 Patent. PF ¶ 1375.

by Example 2. PF ¶¶ 1398–1407. Prof. Myerson explained that the purity of a starting material can have a meaningful influence on the polymorphic outcome of the crystallization. PF ¶¶ 1401–02. The POSA would have thus understood that the experiments submitted to the EPO by Celgene did not replicate Example 2. PF ¶ 1398. The EPO reached the same conclusion and discounted Celgene's experiments accordingly. PF ¶¶ 1400, 1412. Prof. Myerson further explained that Celgene was likely mistaken that it obtained Form C because Form C is a toluene solvate, which can only be made using toluene, which is not a chemical used in Example 2. PF ¶¶ 1404–07.

(2) Example 2 satisfies the enablement requirement for claims 1 and 15 of the '101 Form B Patent.

Example 2 also satisfies the enablement requirement: the experimental evidence from the European proceedings demonstrates that the POSA following Example 2 will make Form B apremilast without undue experimentation. Indeed, that evidence establishes that Example 2 inherently generates Form B, so no experimentation is necessary. Defendants did not dispute that Example 2 was enabling. PF ¶¶ 1422–23.

2. The Asserted Claims of the '101 Form B Patent Are Not Invalid for Obviousness-Type Double Patenting.

Defendants' double-patenting challenge to the '101 Patent largely mirrors their double-patenting challenge to the '638 Patent, and it fails for essentially the same reasons. *See supra* at Section I.D. It is undisputed that the '101 Patent expires later than the '243 Patent only because of a properly awarded statutorily authorized time extension: a PTA of 265 days. PF ¶¶ 1437–47. Accordingly, Defendants' challenge fails as a matter of law—the '243 Patent is not a proper ODP reference. *Ezra*, 909 F.3d at 1375; PF ¶ 1447.

Even were the '243 Patent a proper ODP reference, Defendants' challenge would fail as a matter of equity, PF ¶¶ 1448, 1457, because the challenged difference in expiration dates is not the result of any improper conduct by Celgene. PF ¶¶ 1448–56; *see Breckenridge*, 909 F.3d at 1364.

And it would be inequitable for the improvement claimed by the '243 Patent to cut short the full statutory term of the basic invention claimed by the '101 Patent, solely because of examination delays outside Celgene's control. *See Braat*, 937 F.2d at 593; PF ¶¶ 1457–60.

Even setting aside these threshold failures, Defendants have failed to carry their burden to show that the inventions claimed by Claims 1 and 15 of the '101 Patent are patentably indistinct from the invention claimed by Claim 1 of the '243 Patent. For the purpose of patentable distinctness, "patent claims, being definitions which must be read *as a whole*, do not 'claim' or cover or protect all that their words may *disclose*." *Gen. Foods*, 972 F.3d at 1272. However, the only evidence Defendants presented was the testimony of Prof. Steed, who analyzed what was disclosed by the words of the claims in the '101 and '243 Patents, rather than analyzing the claimed subject matter as a whole, and who (again) did not even mention "distinctness." PF ¶¶ 1461–63. Accordingly, Defendants have not offered sufficient evidence to carry their burden. PF ¶¶ 1461, 1464.

3. Defendants Did Not Prove That Claims 2 and 27 of the '283 Form A Patent Are Invalid as Anticipated or Obvious.

Zydus argues that claims 2 and 27 of the '283 Patent are invalid because the Form A recited in the claims is (1) inherently anticipated by the '052 Publication; and (2) obvious over the '052 Publication, Fieser, Guillory, and Byrn 1994. Zydus's anticipation and obviousness arguments fail because the '052 Publication inherently results in Form B of apremilast, not Form A.

a. Claims 2 and 27 of the '283 Form A Patent are not anticipated.

Zydus argues that Example 2 of the '052 Publication ***inherently*** results in Form A of apremilast. For a reference to inherently anticipate a claim, the claim limitation that is not expressly disclosed in the reference must necessarily and inevitably flow from what is disclosed in the prior art reference. *See Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047–48 (Fed. Cir. 1995).

However, Zydus did not present any experimental evidence that Example 2 of the '052 Publication *ever* produces Form A. Instead, Zydus's sole "evidence" that Form A is inherently produced by Example 2 is Dr. Sacchetti's strained interpretation of two sentences in the specification of the '283 Patent—"In certain embodiments, Form A of [apremilast] can be obtained from various solvents, including, but not limited to, solvent systems comprising acetone, ethanol, and mixtures thereof. In certain embodiments, Form A can be obtained using a fast cooling process." Dr. Sacchetti contends that these two sentences mean that ***any*** recrystallization of apremilast using ***any*** ratio of ethanol and acetone performed using fast cooling will ***always*** produce Form A.

Dr. Sacchetti's reading of this passage is inconsistent with how the POSA would have understood the specification and is disproven by experimental evidence. PF ¶¶ 1508–13. The POSA would have understood that the use of the word "can" in this passage means that Form A ***can*** be made from at least some solvent systems containing ethanol and acetone, and ***can*** be made from at least some recrystallizations using fast cooling. PF ¶ 1509. The '283 Patent does not teach that all ratios of ethanol to acetone will generate Form A and does not teach that a ratio of 2:1 ethanol to acetone will make Form A, whether using fast cooling or not. PF ¶¶ 1508–10. This understanding is confirmed by the experimental evidence of record: all 13 faithful replications of Example 2 used a ***2:1 ratio of ethanol to acetone*** and resulted in Form B, including seven replications that used fast cooling. PF ¶¶ 1473–1507. And nowhere does the '283 Patent state that a 2:1 ratio of ethanol to acetone will make Form A. Zydus misleadingly attempts to frame Amgen's reliance on evidence that Example 2 results in Form B as an implicit admission by Amgen that the '283 Patent is not enabled.[27] Not so. To the contrary, Prof. Myerson explained during cross-

[27] Zydus has ***never*** argued that claims 2 and 27 are not enabled, and cannot do so now. But to be sure, it is not Amgen's position that the '283 Patent fails to enable Form A. Indeed, Amgen commissioned the creation of the Form A reference standard that was used in Dr. Gozzo's testing,

examination that the Form A reference standard used by Dr. Gozzo was made using a ***10:1 ratio of ethanol to acetone***, PF ¶ 1513[28], which is consistent with the just-discussed teachings of the patent. The experimental evidence is clear: Form A is ***never*** made from a 2:1 ratio of ethanol to acetone regardless of the cooling speed (Form B is ***always*** made), but ***other*** ratios of ethanol to acetone (including a 10:1 ratio) using fast cooling may result in Form A. PF ¶¶ 1473–1507, 1512–13.

Dr. Sacchetti concedes that all 13 replications of Example 2 resulted in Form B. PF ¶¶ 1480, 1482, 1484, 1486, 1489, 1491. In contrast, Dr. Sacchetti does not point to a single experiment in which a ratio of 2:1 ethanol to acetone made Form A. Remarkably, he also conceded that he formed his inherent anticipation opinions before he had even seen that experimental data. PF ¶ 1526. Confronted with this evidence, Dr. Sacchetti concocted a theory from whole cloth that the outcomes of all 13 experiments—performed by three different companies in three different laboratories—resulted from inadvertent "seeding"[29] due to the presence of Form B in those laboratories, and that Teva, Zentiva, and Lek/Sandoz did not hot filter or reflux for a sufficient time to prevent seeding. Dr. Sacchetti's speculative theory fails for three reasons.

First, there is no evidence to support it: Dr. Sacchetti conceded that he had no evidence of seeding in any experiment by Teva, Zentiva, or Lek/Sandoz. Dr. Sacchetti speculated that they may have been using Form B, but there was no evidence that any of those companies had used Form B as of the time the experiments were conducted in 2015, much less that Form B had ever

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which was made according to the teaching of the patent using a 10:1 ratio of ethanol to acetone and fast cooling. Zydus's misrepresentation of Amgen's argument is improper and without merit.

[28] Amgen relies only on Prof. Myerson's testimony during cross-examination as the testimony offered by Prof. Myerson in his validity direct examination was stricken. ECF No. 465.

[29] Inadvertent seeding is generally a result of poor laboratory practice, for example failing to clean laboratory equipment, where a crystalline form that was previously used in the laboratory is left-over and unintentionally contaminates later experiments. PF ¶ 1515.

entered any of the laboratories used for the experiments. PF ¶¶ 1516–17. *Second*, Dr. Sacchetti's criticism that the 13 replications did not sufficiently reflux or hot filter is irrelevant because the recrystallization step in Example 2 does not require hot filtration or reflux. PF ¶ 1522. And while Dr. Sacchetti opined that refluxing or hot filtering would have eliminated any inadvertent seeding, there was no evidence to suggest seeding had occurred. PF ¶ 1523. Third, Dr. Sacchetti's seeding theory requires not only that Form B was present in Teva's, Zentiva's, *and* Lek's laboratories, but also that scientists working in all three companies used poor laboratory cleaning practices, PF ¶¶ 1518–19. There is no evidence to support this speculative leap. PF ¶¶ 1514–26.

The experimental evidence proves that Example 2 inherently results from Form B, and that Form A is *never* made from Example 2. Correlatively, Form A is not *always* made, as would be required for inherent anticipation: Indeed, Zydus has not shown that Example 2 of the '052 Publication *ever* results in Form A. Zydus has failed to prove by clear and convincing evidence that the asserted claims of the '283 Patent are inherently anticipated. PF ¶¶ 1472–1526.

b. Claims 2 and 27 of the '283 Form A Patent are not obvious.

Zydus asserts a single obviousness combination against claims 2 and 27: the '052 Publication in view of Fieser, Guillory, and Byrn 1994. Zydus argues that the POSA would have been motivated to perform Example 2 of the '052 Publication using fast cooling to obtain Form A. Importantly, Zydus does not argue that the POSA would have changed any other condition described in Example 2, including the 2:1 ratio of ethanol to acetone. PF ¶ 1527. That is dispositive, because it means that Zydus's obviousness challenge fails for the same reason as its anticipation argument. PF ¶ 1528. Since Example 2 with a 2:1 ratio of ethanol to acetone produces Form B, the '283 Patent claims to Form A are not obvious over Example 2 with a 2:1 ethanol to acetone ratio.

Since the evidence demonstrates that Example 2 inherently results in Form B (regardless

of cooling rate), and Form A ***never*** results from Example 2, Zydus's combination cannot render Form A obvious, because it would have never resulted in Form A.

Moreover, Zydus failed to show that the POSA would have had a reasonable expectation of success in obtaining Form A based on its obviousness combination as of March 27, 2008. Polymorphism is notoriously unpredictable, PF ¶¶ 1529–38, as courts have repeatedly recognized. *E.g.*, *Kowa Co., Ltd. v. Amneal Pharms., LLC*, No. 14-CV-2758, 2017 WL 10667089, at *26 (S.D.N.Y. Sep. 19, 2017), *aff'd,* 745 F. App'x 168 (Fed. Cir. 2018) ("[C]rystallization and polymorphism are unpredictable."); *In re Armodafinil Patent Litig. Inc.* (*'722 Patent Litig.*), 939 F. Supp. 2d 456, 491 (D. Del. 2013) (explaining that "polymorphism is inherently unpredictable" and noting that in 2002, "the unpredictable nature of polymorphism was discussed in publications"); *id.* at 497 ("[T]rial and error crystallization experimentation is necessary because polymorphs are unpredictable."). As the Federal Circuit explained in the context of polymorphs, "'to have a reasonable expectation of success, one must be motivated to do more than merely vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.'" *Grunenthal GmbH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1342 (Fed. Cir. 2019) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007)). Zydus has failed to prove by clear and convincing evidence that claims 2 and 27 of the '283 Patent are invalid as obvious. *See* PF ¶¶ 1527–44.

III. The Asserted Claims of the '541 Titration Patent Are Infringed and Not Invalid.

Sandoz and Zydus have stipulated to infringement of the asserted claims of the '541 Patent. PF ¶¶ 1547–58. The remaining dispute concerns only whether those claims are obvious. PF ¶ 1549. Thus, it is Defendants' burden to show—by clear and convincing evidence—that the POSA would have *modified* the teachings of the prior art to arrive at the asserted claims. *E.g.*, *OSI Pharms., LLC*

v. Apotex Inc., 939 F.3d 1375, 1382 (Fed. Cir. 2019).

Defendants again resort to hindsight by using the claimed titration schedule to select the closest dosing schedule purportedly in the prior art and then arguing that the differences amount to simply "routine optimization." Defendants' expert Dr. Gilmore identified three "key references" for obviousness: the '536 Patent, Papp 2012, and Schett 2012. Trial Tr. at 831:20–832:3 (Gilmore Direct 6.21.21). But Defendants' expert failed to address *why* the POSA would have forgone the conventional approach to dose titration in favor of making the very specific changes necessary to arrive at the claimed dosing schedule, and Defendants' expert failed to explain *why* "optimization" would have resulted in the claimed schedule, which has multiple significant differences from the prior art. For several independent reasons, Defendants failed to carry their heavy burden.

A. The POSA Would Have Titrated Apremilast on an Individualized, Feedback-Driven Basis Over a Period of Weeks.

The conventional approach to dose titration in 2014 was to titrate a medication on an *individualized, feedback-driven* basis, with the physician tailoring the schedule for each patient based on that patient's characteristics (such as age and weight) with adjustments made as treatment continues based on patient-specific feedback (such as the patient's response to the treatment in terms of safety, efficacy, and tolerability). PF ¶¶ 1553–60, 1592–1605, 1617–20. The duration of conventional titration was typically several weeks to several months.

The evidence adduced at trial is replete with teachings and examples following the convention of individualized, feedback-driven titration. The '536 Patent, for example—a reference Defendants chose to identify as "key" prior art—describes methods of treating psoriasis by dosing apremilast according to the characteristics of each patient:

> ***The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient.*** Suitable dosing regimens can be readily selected by those skilled in the art ***with due consideration of such factors***.

JTX-7 at 13:45–64 (emphases added); *see also id.* at 13:59–63 ("In managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 25 mg, and increased ***if necessary*** up to about 200 mg to about 1000 mg per day as either a single dose or divided doses, ***depending on the patient's global response***.") (emphases added); PF ¶¶ 1563–68, 1603–05. The plaque psoriasis patient population is very diverse in terms of age, weight, comorbidities, and gender. PF ¶ 1557. The trial evidence also showed that drugs other than apremilast that were titrated—used to treat psoriasis or other conditions—were routinely titrated in a fashion tailored to each individual patient. PF ¶¶ 1553–60, 1592–1602.

The claims of the '541 Patent are directed to a dramatically different approach. The '541 Patent instructs "administering" apremilast according to a specific and complete dose titration schedule. JTX-13 at 31:3–26. The claims do not set forth any steps for tailoring the titration schedule based on the patient's individual characteristics, test results, or feedback. PF ¶¶ 1585–87. The claimed approach is valuable because it is convenient for both doctor and patient by reducing or eliminating the need for consultations during the titration process and reducing patient confusion and uncertainty about how to take the medication. PF ¶¶ 1561–63.

Defendants' trial presentation simply ignored all of this evidence and asserted that the POSA would have looked to the titration schedules used in prior art clinical trials (*i.e.*, Phase 2 studies reported in Papp 2012 and Schett 2012) and then would have been motivated to make modifications to those that precisely arrived at the claimed dose titration schedule. PF ¶¶ 1591, 1608–45. Defendants failed to articulate a reason for why the POSA—who under both sides' definition is a *treating physician*—would have favored titration techniques peculiar to the artificial clinical trial setting over the conventional titration approach consistently taught in the prior art related to *treating patients*, which is the focus of the '541 Patent. The POSA in 2014, considering

an apremilast titration schedule for use in a method of treating patients with psoriasis, (1) would not have been inclined to adopt a pre-determined and one-size-fits-all titration schedule, (2) would not have sought to modify either of the titration schedules identified by Defendants, and (3) assuming for the sake of argument that the POSA would have departed from the conventional approach to titration, the POSA would not have reasonably arrived at the claimed titration schedule given there were innumerable pre-determined and one-size-fits-all titration schedules possible.

B. The POSA Would Never Have Modified Papp 2012.

Instead of addressing the convention of individualized, feedback-driven titration reflected in the prior art, Defendants' hindsight-driven assumption was that the POSA would have focused solely on pre-determined, one-size-fits-all titration. In that regard, Defendants' central theory appears to have been that the POSA would have modified Papp 2012—one of the only prior art references which even arguably disclosed a pre-determined, one-size-fits-all titration schedule—to arrive at the claimed invention. *See, e.g.*, Trial Tr. at 858:11–859:25 (Gilmore Direct 6.21.21).

As an initial matter, Defendants did not even establish that the POSA would have known the specifics of the "Papp 2012 schedule." Papp 2012 is an article reporting on a Phase 2 clinical study of apremilast for the treatment of psoriasis, which included multiple treatment arms: patients titrated to 10 mg twice daily, 20 mg twice daily, 30 mg twice daily, and placebo. PF ¶ 1569. But Papp 2012's description of titration for all study arms is terse: "Doses were titrated in the first week to mitigate potential dose-dependent adverse events of apremilast; all patients reached the target dose by day 5."[30] DTX-153 at DTX-153_2. The POSA reading Papp 2012 therefore would

[30] Defendants' attempt to backfill this gap with the Pathan reference on ankylosing spondylitis is unavailing. Papp 2012 and Pathan describe their titration schedules differently, PF ¶ 1576–77, and Celgene was known to have used different titration schedules from study to study, particularly across disease states, as is evident from Papp 2012 (titration implemented over five days at most) and Schett 2012 (titration implemented over seven days at most), *see* PF ¶¶ 1573, 1582.

not even have known whether the titration employed was pre-determined or one-size-fits-all, let alone what specific titration schedule, if any, was used in that study. PF ¶¶ 1573–77. Numerous possible titration schedules would have been consistent with Papp 2012's brief disclosure, and the POSA would not have known which of them, if any, had actually been used. PF ¶¶ 1573–77.

Even assuming erroneously both that the POSA would have departed from the conventional approach to titration and that the POSA somehow knew the details of the undisclosed titration schedule of Papp 2012, Defendants did not meet their burden of proving that the POSA would have been motivated to *modify* that schedule *at all*, much less modify it in all of the ways needed to somehow arrive at the claimed invention. *See, e.g.*, *OSI Pharms.*, 939 F.3d at 1382. The Papp 2012 authors expressed no dissatisfaction with the tolerability results from the study, reporting that the treatment was "generally well-tolerated." DTX-153 at DTX-153_2, 7; PF ¶ 1609. The POSA would have given significant weight to the conclusions of the Papp 2012 authors, given that the article was published in *The Lancet*—a top-tier journal—and the first-listed author is a recognized thought-leader in the field. PF ¶ 1610. Accordingly, even granting all of Defendants' erroneous assumptions above, the POSA would have simply adopted the schedule that had been successfully used in a Phase 2b clinical trial. PF ¶¶ 1608–11.

C. Any Departure from the Papp 2012 Schedule Would Have Extended Titration By Weeks, Not One Day.

Even incorrectly assuming for the sake of argument both that the POSA would have chosen to titrate according to a pre-determined, one-size-fits-all schedule *and* would have been motivated to modify the Papp 2012 schedule—Defendants still failed to show that the asserted claims are obvious. The evidence showed that any modification to Papp 2012 would have extended the titration schedule by ***several weeks to a month***, not a single day. PF ¶¶ 1612–28.

The uncontroverted record reflects that in the prior art and actual practice of physicians

treating patients, titration conventionally takes place over multiple weeks or months. PF ¶¶ 1553, 1556–60, 1596–97, 1617–20. For example, a reference directed to methods of treating patients using apremilast, WO '102, teaches titrating apremilast as a multi-week process. Prior art labels for other drugs likewise describe titration schedules on the orders of weeks, not days.

Dr. Gilmore's testimony did not provide a pertinent or corroborated reason why the POSA would have extended any prior art titration schedule by a single day as opposed to weeks. PF ¶¶ 1612–28. Dr. Gilmore opined that the POSA would have been motivated to add a single day to the Papp 2012 schedule "to reduce some of the side effects . . . which were identified within the first two weeks of treatment within the Papp trial." Trial Tr. at 859:13–21 (Gilmore Direct 6.21.21), 858:11–16 ("A POSA would look to perhaps decrease the magnitude of the dose increases during the initial titration schedule, perhaps start at a lower dose to help ameliorate some of those adverse effects -- events."), 862:25–863:7 (compared to the Papp 2012 schedule, the '541 Patent "would be more comfortable for the patient"). She further testified that there was *nothing* "in the prior art indicating that you would want a longer titration [than seven days] that the POSA would have relied upon." *Id.* at 864:13–19 (Gilmore Direct 6.21.21). PF ¶ 1622. That is simply wrong. Papp 2012 itself taught this, stating that "at least *half* of [adverse] events occurred within *2 weeks* of treatment initiation and resolved within a *week*," indicating that adverse events were recorded for at least three weeks, and perhaps longer. DTX-153 at DTX-153_7 (emphases added). The evidence established that, if the goal was to make apremilast more tolerable by extending the titration period, the POSA would have extended the titration duration by multiple weeks. PF ¶¶ 1612–28.

The ***only*** titration schedules of one week or less identified by Defendants are those of Papp 2012 ("by day 5") and Schett 2012 ("during the first 7 days"). Both references, however, arise from the clinical trial setting, not from treating patients in the real world. *E.g.*, PF ¶¶ 1569–88. Dr.

Gilmore's only attempt to explain why the POSA would have been motivated to titrate over a period measured in days not weeks was a purported need "in the environment of a clinical trial . . . to get to your goal dose so that you can start to accumulate data on the treatment." Trial Tr. at 863:8–17 (Gilmore Direct 6.21.21); *see also* PF ¶¶ 1621–27. Dr. Gilmore never explained by what point in time one would need to "start to accumulate data," why one could not "accumulate data" while titrating the dose for additional days or weeks, or whether her testimony was rooted in any FDA or other regulatory requirement. In any case, considerations of clinical trial design and regulatory approval are wholly irrelevant here. Both sides' POSA definitions are drawn to physicians who treat patients, not a clinical trialist or similar person who would have been qualified for and interested in designing a clinical trial. And no expert was tendered, let alone accepted by the Court, to provide expert opinions related to clinical trial design or FDA regulatory processes. While the POSA may well have been interested in learning ***the results*** of clinical trials ***to inform treatment decisions***, the evidence showed that the POSA would not have been constrained or otherwise influenced by clinical trial data collection or design in arriving at a titration schedule.

Indeed, Dr. Gilmore agreed that a 28-day titration schedule would be more tolerable than a 5, 6, or 7-day schedule. PF ¶ 1620. The evidence also showed there was no motivation pushing meaningfully towards a short titration period for apremilast; within reasonable bounds (*i.e.*, a month out), clinical efficacy would not have been a consideration for the POSA deciding how long to titrate apremilast. PF ¶ 1628. Dr. Gilmore made this clear. She testified *first* that tolerability, not efficacy, would have been the POSA's concern in designing a titration schedule; and *second*, that the POSA in 2014 would have understood that it generally takes months for apremilast to exhibit efficacy in patients. Thus, the trial evidence showed that the POSA would have seen a benefit for tolerability, ***and no drawback for efficacy***, in adopting a multi-week titration schedule for

apremilast, which of course would have taken the POSA far beyond the six-day schedule of the asserted claims. It is, therefore, another example of hindsight bias when Dr. Gilmore contradicts the prior art and states, without support, that the POSA would have considered a one-day extension when seeking to address dose-dependent side effects associated with apremilast.

Indeed, Dr. Gilmore's own prescribing practices for apremilast are consistent with the evidence and refute her contrary opinions. Dr. Gilmore, a POSA in 2014, began prescribing Otezla shortly after its launch in 2014. Trial Tr. at 908:5–8 (Gilmore Cross 6.21.21). Initially, Dr. Gilmore instructed her patients to follow the titration schedule on the Otezla label—the schedule claimed by the '541 Patent. Trial Tr. at 908:9–14, 909:9–15, (Gilmore Cross 6.21.21); 948:2–6 (Gilmore Redirect 6.21.21). But when Dr. Gilmore decided to depart from the titration schedule on Otezla's label in or about 2017, Dr. Gilmore extended titration to 29 days in an effort to improve tolerability (the "Gilmore Schedule"). PF ¶ 1626; *see also* Trial Tr. at 947:20–24 (Gilmore Redirect 6.21.21). Thus, as further evidence of hindsight bias, while Dr. Gilmore opined at trial in 2021 (without support and contradicting multiple relevant teachings in Papp 2012) that the POSA in 2014 would have extended a five-day titration by a single day in an effort to improve apremilast's tolerability, Dr. Gilmore herself in 2017 extended a six-day titration *by more than three weeks* when seeking to achieve the same objective. In fact, Dr. Gilmore could not even remember having *considered* a one-day extension when she first decided to alter the Otezla schedule. PF ¶ 1626.

To the extent that Defendants attempt to reconcile Dr. Gilmore's testimony by asserting that she had personal clinical experience with apremilast not available to the POSA, *e.g.*, Trial Tr. at 948:7–949:6 (Gilmore Redirect 6.21.21), that argument has no merit. While Dr. Gilmore's prescribing practices are inconsistent with Defendants' hindsight-driven obviousness argument, they are *fully consistent* with the record evidence that the POSA in 2014 would have titrated

apremilast over multiple weeks. Defendants also did not establish that the information available to Dr. Gilmore in 2017 was meaningfully different from the information and conventional practices known to the POSA in 2014. Dr. Gilmore never claimed to have based her adoption of the Gilmore Schedule on any published information—about titration or otherwise—that did not already exist in 2014. Rather, the sole purported basis for the Gilmore Schedule was the anecdotal experience of her own patients. Thus, Dr. Gilmore in 2017 stood in largely the same position as the POSA in 2014. The Court is certainly entitled to consider the fact that Dr. Gilmore's own design choice in 2017 diverged so dramatically from the one she ascribes to the POSA in 2014. *See, e.g.*, *In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1025 (Fed. Cir. 2018) ("The district court also properly relied on [post-priority-date] Khan 2009 not as statutory prior art, but for the fact that POSITAs were interested in pursuing less frequent dosing regimens.").

D. Defendants Failed to Explain How the POSA Would Have Arrived at the Claimed Schedule in Particular from Among Many, Many Possibilities.

Amgen's expert, Dr. Alexis, identified *at least* nine relevant variables of a pre-determined, one-size-fits-all dose titration schedule. That variability would have led to an enormous number of possible titration schedules, PF ¶¶ 1629–33, and Defendants failed to explain why the POSA would have been motivated to arrive at the claimed one in particular or have had a reasonable expectation of success in doing so given the many possibilities.

Informed by hindsight, Defendants cherry-picked characteristics of the Phase 2 schedules that Dr. Gilmore ascribed to Papp 2012 and Schett 2012—and combined them with characteristics ***in neither*** Phase 2 schedule—to arrive at the claimed schedule. This approach is without merit, as there is no evidence that the POSA would have adopted such a mix-and-match approach rather

than default to the conventional approach of individualized and feedback-driven titration.[31]

There are multiple substantial differences between the titration schedules used in the apremilast Phase 2 studies, and the schedule claimed in the '541 Patent. PF ¶¶ 1635, 1637. For example, even assuming the POSA had known the details of the titration schedule used in the Papp 2012 study, Dr. Gilmore admitted there were "major" differences with respect to that schedule, including different: (1) starting doses, (2) dose increments, and (3) lengths of titration. Trial Tr. at 860:19–861:9 (Gilmore Cross 6.21.21). Similarly, the distinctions between the Schett 2012 schedule and the claimed schedule are myriad. Such distinctions include, for example, the day on which the target dose is reached, the target dose level, the number of daily increments in dose, the size of the increments, the uniformity or non-uniformity of increments, the length of time between increments, the uniformity or non-uniformity of the length of time between increments, the uniformity or non-uniformity of morning and afternoon doses, and once-daily versus twice daily dosing. Neither of the Phase 2 schedules teaches other aspects of the claimed schedule, such as, for example, reaching maintenance *on day 6*, initiating treatment at 10 mg *in the morning* (and nothing in the afternoon), or increasing the daily dose *each day*. PF ¶¶ 1633, 1635, 1637.

Defendants asserted that the POSA would have adopted (only) Schett 2012's Day 1 dose of 10 mg and certain characteristics of the Papp 2012 schedule, while *ignoring* all the many other differences between those schedules and the claimed schedule. PF ¶¶ 1633–36. Defendants did not provide any evidence establishing that the POSA would have mixed-and-matched these aspects of the two titration schedules used in the different clinical studies reported in Papp 2012 and Schett

[31] Defendants did not suggest at trial that the POSA would have started with Schett 2012 and then modified it. And for good reason. Schett 2012 explains that the tested treatment was "generally well tolerated" and "provides strong evidence of the efficacy of apremilast for the treatment of active [psoriatic arthritis], with a more balanced profile of efficacy, tolerability, and safety relative to that of other PDE4 inhibitors." DTX-162 at DTX-162_1, 10.

2012 or selected just these specific aspects of those titration schedules over others that would have taken the POSA further away from the claimed invention. *E.g.*, PF ¶¶ 1636, 1638.

Without any rationale for how the prior art would have led the POSA to design any particular schedule, Defendants resort to hand-waving about "routine optimization" to bridge the gap between Papp 2012 and the claimed invention. Trial Tr. at 858:11–20, 859:13–25, 861:10–15 (Gilmore Direct 6.21.21). But invoking "routine optimization" cannot substitute for a proper obviousness analysis, nor discharge Defendants' burden of clear and convincing evidence. This is not a case of overlapping ranges of the sort typically at issue in "optimization" cases. *See, e.g.*, *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) ("Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. . . . [B]ecause the prior art disclosed values ***overlapping the claimed ranges***, the 'general conditions' of the claim are disclosed.") (emphasis added).

Here, no prior art encompasses a predetermined, one-size-fits-all 6-day titration schedule reaching 30 mg twice daily. *See, e.g.*, PF ¶¶ 1635–38. In fact, as discussed above, a titration schedule is defined by *numerous* variables—not simply the length of titration, and the POSA would have needed to select the correct criterion for each of those variables before arriving at the claimed schedule. PF ¶¶ 1630–33. Moreover, the evidence shows that the universe of possible pre-determined, one-size-fits-all titration schedules is so large—and the effort to determine which would be the best schedule so onerous—as to undermine Defendants' reliance on "optimization" alone to try to make an obviousness case. *See, e.g., Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011) ("The facts here present a case where the disclosed range is so broad as to encompass a very large number of possible distinct compositions thus requiring nonobvious invention . . . .") (cleaned up). Nor is this a case where the prior art

disclosed a "finite number of identified, predictable solutions." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1332 (Fed. Cir. 2014) (quoting *KSR Int'l*, 550 U.S. at 421).

To illustrate some of the numbers of possible dose titration schedules, Dr. Alexis designed a set of parameters for titration schedule variables that would have been reasonable for the POSA to consider based on the prior art and the POSA's knowledge. PF ¶¶ 1639–45. Such parameters included, for example, that the maintenance dose reached 30 mg twice daily, that doses only increase over time, and that apremilast could be dosed in increments of 5 mg (as taught in Defendants' key '536 Patent reference as well as other prior art).[32] PF ¶¶ 1640–41. Even when adopting Dr. Gilmore's unwarranted assertion that the maintenance dose is reached on day 6 as an additional criterion, there are more than ***70,000*** possible dosing titration schedules. PF ¶ 1642. And, even if the POSA is given nearly every limitation in the claimed titration schedule, which would never have happened and is entirely improper as a matter of law, there are still ***eighteen different possibilities***. PF ¶ 1644. And of course, if one were to expand the 6-day criterion to allow for titration of up to twenty-nine days like the Gilmore Schedule (which Dr. Gilmore agreed the POSA would find reasonable), the numbers of possible titrations again expand dramatically. PF ¶ 1643.

Thus, attempting to "optimize" the prior art would not have been "routine" as Defendants assert. PF ¶ 1645. The POSA would not have been drawn to any particular schedule, but instead would have needed to test each of them. The POSA also would not reasonably have expected that any one of the possible titration schedules would be an optimized titration schedule. PF ¶ 1645.

[32] Dr. Gilmore agreed the POSA would not have been limited to 10, 20, and 30 mg dosage forms, but noted that the '536 Patent lacks the sort of clinical data included in Papp 2012 and Schett 2012. Trial Tr. at 834:11–13 (Gilmore Direct 6.21.21). Dr. Gilmore never explained why clinical data would lead the POSA to select only dosages that are multiples of 10 mg rather than 5 mg.

E. The Claimed Dosing Schedule Provides Benefits to Physicians and Patients.

Amgen's expert Dr. Alexis testified that the patented titration schedule has delivered real benefits for patients in the form of clarity in instruction, convenience, and overall "very favorable" experience. PF ¶¶ 1561–63. With the individualized and feedback-driven titration approach that was convention in 2014, there were patients that experienced anxiety and uncertainty about their treatment from visit to visit. The claimed titration schedule allows patients to know exactly what to expect during the entirety of their titration and know exactly when they will reach the maintenance dose. Physicians benefit from the claimed titration schedule because, for example, they do not need to spend unnecessary time monitoring lab results and meeting with patients in order to get the patients up to their maintenance dose. PF ¶ 1561.

Defendants have made much of the fact that, during patent prosecution, Celgene introduced unexpected results—clinical data showing tolerability improved with the patented titration schedule compared to the schedules used in the Phase 2 trials reported in Papp 2012 and Schett 2012.[33] Defendants' insinuations that the absence of such unexpected results in this trial supports their obviousness position are wrong as a matter of law and therefore irrelevant. PF ¶¶ 1646–51.

First, the *absence* of objective indicia is *not* evidence of obviousness. *Miles Labs., Inc. v. Shandon Inc.*, 997 F.2d 870, 878 (Fed. Cir. 1993) (absence of objective indicia "does not weigh in favor of obviousness"). Accordingly, Dr. Scharfstein's testimony, which dissected the unexpected results presented during prosecution, is irrelevant and should be excluded for the reasons stated on

[33] Amgen cannot be faulted for choosing not to put forward evidence of objective indicia supporting non-obviousness of the '541 Patent claims in order to focus its trial presentation. Furthermore, Dr. Scharfstein was apparently misreading certain statements regarding statistical significance in the file history of an unrelated patent when he accused Celgene of making untrue representations to the Patent Office. PF ¶ 1651. That erroneous accusation should be disregarded.

the record. Trial Tr. at 803:18–804:4, 809:18–811:20 (Attorney Argument 6.21.21).

Second, Defendants' assertion[34] that the Patent Office only allowed the '541 Patent because of the unexpected results evidence is false. The '541 Patent's file history shows unexpected results were introduced as an alternative argument, in the event the Examiner did not find applicant's argument against *prima facie* obviousness persuasive. PF ¶ 1650. Later, the Examiner withdrew all pending rejections, including the one to which the unexpected results evidence was responsive, as "moot," while interposing new rejections based on different issues. JTX-24 at JTX-24_1083. After those rejections were overcome, the Examiner allowed the patent and *made no mention* of unexpected results in the statement of reasons for allowance. PF ¶¶ 1648–49. Defendants presented no testimony that unexpected results was the but-for cause of allowance, *see, e.g.*, Trial Tr. at 994:1–22 (Scharfstein Cross 6.21.21), presumably because no witness could testify to that effect.

CONCLUSION

Amgen respectfully requests that the Court enter judgment that each asserted claim is (i) infringed by each Defendant against whom the claim is asserted and (ii) is not invalid.

[34] *See* Trial Tr. at 70:12–71:6 (Defendants' Opening Statement) ("unexpected results . . . got them the patent"); Trial Tr. at 804:24–805:14 (Attorney Argument) (Defendants' statement that the reason "they got the '541 patent" was by arguing that the claimed schedule showed unexpected results over the Papp 2012 schedule).

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Respectfully submitted,

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